

PLATE I

- | | | |
|--|--------------------|--|
| 1. <i>Entamæba histolytica</i> . | } $\times 1,000$. | 17. <i>Enterobius vermicularis</i> $\times 350$. |
| 2. <i>Entamæba histolytica</i> cyst; in saline. | | 18. <i>Gastrodiscoides hominis</i> $\times 275$. |
| 3. <i>Entamæba histolytica</i> cyst; iodine stained. | | 19. <i>Schistosoma mansoni</i> $\times 200$. |
| 4. <i>Entamæba coli</i> . | | 20. <i>Schistosoma hæmatobium</i> $\times 200$. |
| 5. <i>Entamæba coli</i> cyst; in saline. | | 21. <i>Echinococcus</i> $\times 7$. |
| 6. <i>Entamæba coli</i> cyst; iodine stained. | | 22. <i>Aëdes ægypti</i> $\times 5$. |
| 7. <i>Trichomonas hominis</i> . | | 23. <i>Glossina palpalis</i> $\times 2$. |
| 8. <i>Giardia</i> . | | 24. <i>Phlebotomus papatasi</i> } $\times 6$. |
| 9. <i>Giardia</i> cyst. | | 25. <i>Phlebotomus argentipes</i> } |
| 10a. <i>Filaria bancrofti</i> . | } $\times 350$. | 26. <i>Pediculus humanus</i> $\times 8$. |
| 10b. <i>Filaria malayi</i> . | | 27. <i>Dermacentor andersoni</i> $\times 6$. |
| 11. Hookworm ova. | | 28. <i>Trombicula akamushi</i> , adult $\times 8$.
(Nymph inset) |
| 12. <i>Ascaris</i> ova (fertilized). | | 29. <i>Xenopsylla cheopis</i> $\times 8$.
(Actual size of insects inset in ring) |
| 13. <i>Ascaris</i> ova (unfertilized). | | |
| 14. <i>Trichuris trichiura</i> . | | |
| 15. <i>Tænia saginata</i> . | | |
| 16. <i>Fasciolopsis buskii</i> . | | |

The approximate magnification of each figure is shown.

PLATE II

(Giemsa's stain : $\times 2,000$)

- A. Benign tertian (*Plasmodium vivax*)
Young ring form; amœboid trophozoite; three-quarter-grown trophozoite; developing schizont; dividing schizont; male gametocyte; and female gametocyte.
- B. Malignant tertian (*P. falciparum*)
Young ring form; four ring forms, including one accolé form, in one red cell; band form; a larger ring form with Maurer's dots; mature schizont, or rosette; male crescent; and female crescent.
- C. Quartan (*P. malariae*)
Young ring form; young band form; large band form; schizont; merozoites (free); male gametocyte; and female gametocyte.
- D. (*P. ovale*)
Young ring form; band form; two schizonts in one corpuscle; infected corpuscle showing a fimbriated outline; dividing schizont; male gametocyte; and female gametocyte.
- E. Trypanosomes
(a) *T. gambiense*. (b) *T. brucei*. (c) *T. cruzi*.
- F. Bartonella.
- G. *Spirillum minus*.
- H. *Treponema recurrentis*.
- I. Leishmania
(a) 'Round' forms (Leishman-Donovan bodies) from spleen puncture.
(b) 'Torpedo' forms of Leishman-Donovan bodies.
(c) The flagellate forms.
- J. *Leptospira icterohæmorrhagiae* (the rope-like spirals would not show in a Giemsa-stained specimen).
- K. Comma bacilli.



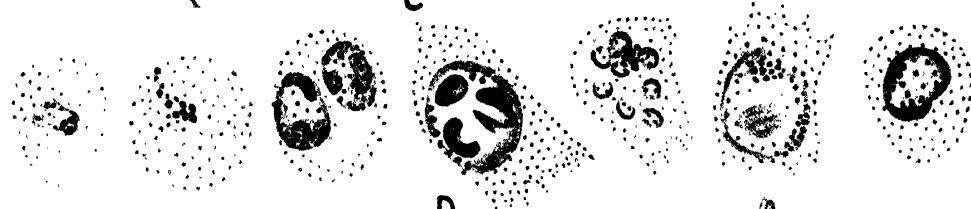
A



B



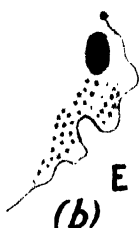
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D



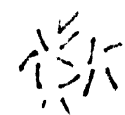
(a)



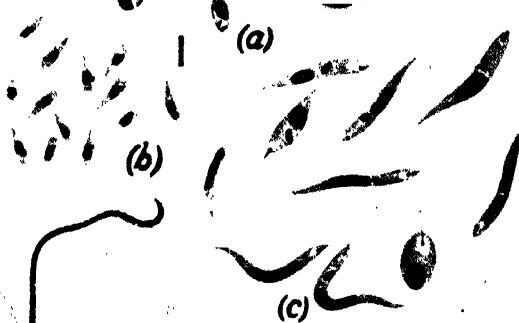
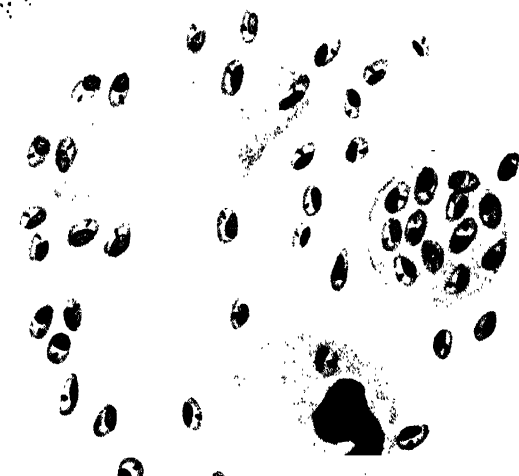
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(c)



F

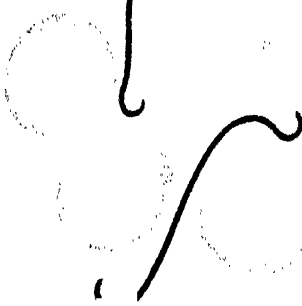
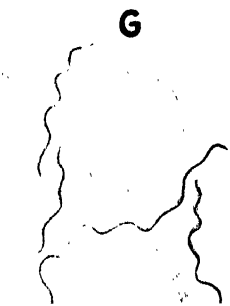


(a)

(b)

(c)

G



I



K

H.R

THE
PRINCIPLES AND PRACTICE
OF
TROPICAL MEDICINE

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THE PRINCIPLES
AND PRACTICE
OF TROPICAL
MEDICINE

P R E F A C E

Apologia.—There are several excellent books on tropical medicine, and the writer who proposes to add yet another book on this subject must make some attempt to justify his action, particularly in times of paper shortage. The writer of this book has been engaged in teaching tropical medicine for about seven years; it is perhaps not unnatural that he should have evolved his own method of presenting the subject, and that, after writing and rewriting his lecture notes many times during these years, he should conceive the not very original idea of putting these notes into book form, so that his, and perhaps other, students could digest them at their leisure. If any further excuse is required, it is that, towards the end of 1941, there was in India an acute shortage of new copies of the standard books on tropical medicine, a shortage that seemed as if it might be lasting. Since that time, of the three best books on tropical medicine, new editions of two have appeared, and the third has been reprinted; it was then too late to turn back, and the writer can only hope that his presentation will have some special appeal for at least a few readers.

THE EMPHASIS IN TROPICAL MEDICINE

About a year ago, a number of army medical officers arrived in India from Great Britain and the United States, and, in order to initiate them into medical practice in the tropics, classes were organized; it fell to the writer to conduct some of these classes. By way of introduction to his lectures, he attempted to analyse the difference between medical practice in temperate climates, for which most of these men had received their training, and practice in the tropics, which was to be their lot for a time at least. Is it, he wondered, just that different diseases are encountered? Surely, the difference is a deeper, more significant one; otherwise, it would only be a matter of extending one's reading to include the rarer tropical diseases that are usually omitted from the more concise textbooks of medicine. He believes that the main difference lies rather in the special emphasis given to certain aspects of those diseases that are looked upon as tropical diseases. What are the special emphases, and what are the reasons for them? It will perhaps be worth considering a few of these, and it will be more convenient to take them up in the order in which they are usually presented rather than in the order of their importance.

History.—Tropical medicine is a young, rather self-conscious branch of medical science; much of its history has happened within the lifetime of the older writers, and, even when the writers themselves have played little part in the historical events, they often knew the principal actors personally. But this emphasis on history is more than an exhibition of self-consciousness, with perhaps some concession to personal vanity. The history of a disease and of the discovery of its ætiology forms a necessary background for the proper appreciation of the present state of knowledge, which must never be looked upon as final, however complete it appears to be.

Epidemiology.—The diseases of Aberdeen are much the same as those of London, or even of New York, Berlin, or Vienna, and although respiratory diseases may be more common in the winter, and certain infectious diseases at other seasons, there is no sharp segregation to any one time of year of the bulk of the diseases with which the practitioner in temperate countries has to deal. Diseases in the tropics however show marked variations from

place to place, and from season to season. Therefore, it is necessary to know as much about the epidemiology as possible, and at least roughly the geographical and seasonal distribution of each disease, so that one knows how, where and when to expect to encounter the disease, and does not lightly diagnose kala-azar in central Africa, sleeping sickness in India, plague in the Punjab in July, or sand-fly fever anywhere in the northern hemisphere in January.

Ætiology and prevention.—The bulk of the diseases that one encounters in temperate climates are degenerative or chronic inflammatory diseases, the prevention of which is outside the scope or even the thoughts of the average practitioner, so that he has no further worry on this score, and, even when he does encounter an infectious disease, whether it is measles, influenza, or just a common cold, there is seldom much mystery about the mode of infection, which in any case is by direct contact and/or droplet infection; he has only the household, or, in the case of an institution, the other inmates to consider, and after that, the most he need do will be to notify the local medical officer of health. On the other hand, nearly all tropical diseases are of an infective nature and eminently preventable, so that the practitioner's thoughts should be for the community as much as for the patient; he must have a thorough knowledge of the ætiologies of the infections that he may encounter, if he is to appreciate the significance of his diagnosis and to take the rational steps to prevent the disease spreading. But the mode of transmission of tropical diseases is seldom simple and straightforward, for there is often not only the parasite itself but also an insect vector, an intermediate host, and/or an animal reservoir of infection. In fact, with the exception of 'diseases due to the direct effects of a tropical climate' and the 'intestinal fluxes', all the diseases dealt with in this volume are transmitted from or through an animal and/or an insect. This is the type of problem that the practitioner in the tropics may have to face. Is it Weil's disease? If so, he will think, it would be interesting to know how in this case the infection was acquired, and whether there was an occupational association, but he should know that in the tropics it is often a sporadic disease, so that he need not do anything further about it, and will be free to turn his full attention on the patient. Is it dengue? If so, perhaps this indicates the beginning of the dengue season; he will have to expect more cases, if not an epidemic, and he will have to make his plans accordingly. Or is it yellow fever? If it is, and if the disease has not appeared here before, then he must give his full attention to averting a major disaster; after putting the patient under a mosquito net, he must organize an anti-aedes campaign immediately, and take other necessary steps.

The practitioner in the tropics is so often alone, and responsible for prevention as well as cure, but, even if he is not, for his own, for his family's or for his hospital personnel's sake, he can never escape giving prevention an immediate thought. So, perhaps most of all, the practitioner in the tropics must have a thorough knowledge of the ætiology of all the diseases he is likely to encounter.

Signs and symptoms versus laboratory findings.—The populations with which one has to deal in temperate countries are usually relatively homogeneous, but in the tropics they are often heterogeneous, in racial type, in economic status and nutrition, and in their previous experience of diseases; consequently their response to infection will be equally varied. When the Cumberland miner gets pneumonia, the disease will run very much the same course as it would in a London banker, and it is possible to give a clinical description that will cover both cases. But it is not so with the vast majority of tropical infections; a patient may react to malaria

infection in a hundred different ways, and, further, the story told by the illiterate patient, even if the language and dialect difficulty can be overcome, is often misleading, so that one is compelled to lay less emphasis on signs and symptoms and more on laboratory findings.

Again, in temperate climates, although there are a few diseases in which one seeks confirmation from the bacteriologist, the average practitioner's clinical laboratory work begins and ends with urine analysis; whereas the vast majority of tropical diseases are protozoal or metazoal in origin, and these diseases lend themselves to easy and accurate parasitological diagnosis, so that, once more, emphasis is thrown on laboratory findings.

In temperate climates one is taught that it is usually safer to make one diagnosis, and to attempt to trace all the signs and symptoms to a single infection or pathological process; whereas, in the tropics, single infections are the exception, and, even when one infection has been discovered, it is as important and necessary to carry out routine laboratory examinations of, at least, the stools, the urine, and the blood, as it is to make a thorough physical examination, and to examine the patient's chest even when most of the symptoms point to the abdomen.

On the other hand, very great care must be taken that one's clinical judgment is not outweighed by laboratory findings. For example, it is not uncommon to find microfilariae in the blood, and hookworm ova and *Entamæba histolytica* cysts in the stools of a patient in whom kala-azar is eventually diagnosed by sternum puncture. Although each finding might be significant in other circumstances, there may in the particular case be no signs or symptoms attributable to these infections, and, although in most instances one would attempt to free the patient from his hookworm infection during his convalescence after treatment for kala-azar, return to normal health may be possible without the eradication of any of these infections.

Laboratory findings may be as misleading in some cases as they are useful and even essential in others, and, although the writer is in favour of routine laboratory examinations whenever it is possible to carry these out, it is very necessary that the findings should be given their proper perspective, viewed in conjunction with the whole clinical picture, and interpreted intelligently. The writer's early experience of tropical medicine was all in the laboratory, and even in those days he saw the danger of the complete laboratory domination of tropical practice, and he has fought very hard against this tendency ever since. He hopes that in this book, whilst emphasizing the great importance of the laboratory, he has succeeded in keeping it in its proper place.

Specific treatment.—Finally, in the matter of treatment, tropical medicine undoubtedly stole a march on the mother science. We had specifics for malaria, kala-azar, sleeping sickness, and certain helminth infections, not to mention the tropical spirochætal infections, when 'temperate' medicine could claim only salvarsan, unless one includes anti-venine and diphtheria antitoxin, one for each side. Although the sulphonamides and newer chemotherapeutic substances have gone some way to even up matters, case for case, specific treatment is far more important in tropical than in temperate medicine. Moreover, in tropical practice, conditions are often such that specific treatment is the only treatment that can be considered, and it is therefore given emphasis, often to the detriment of general and symptomatic treatment which in many circumstances is almost if not quite as important.

LITERATURE

The writer would have been failing in his duty, if in writing this book he had not made free use of the existing textbooks of tropical medicine,

especially Rogers and Megaw's *Tropical Medicine*, Manson-Bahr's *Manson's Tropical Diseases*, and Strong's *Stitt's Tropical Medicine*; the last-named very full and up-to-date textbook unfortunately only arrived in India when the manuscript for the present volume was almost complete. Scott's *History of Tropical Medicine* and the appropriate chapters in the *British Encyclopædia of Medical Practice* were also used freely. As for the periodicals, the special journals, the *American Journal of Tropical Medicine*, the *Transactions of the Royal Society of Tropical Medicine*, the *Annals of Tropical Medicine and Parasitology* and the *Archive für Schiffs- u. Tropen-Hygiene*; the local journals, the *Indian Medical Gazette*, the *Indian Journal of Medical Research*, and the *Records of the Malaria Institute of India*; and of the general medical journals, the *Journal of the American Medical Association*, the *Lancet*, and the *British Medical Journal*, the *Bulletin of the Health Organization of the League of Nations*, and of course above all the comprehensive *Tropical Diseases Bulletin* have provided the most useful material.

REFERENCES

There is no satisfactory solution to the problem of references in a book of this kind. It would be out of the question to cite all important work on each subject, and yet on the other hand there are few subjects about which our knowledge has become so standardized that one can be entirely impersonal. Some of the authors of books on tropical medicine refer to other workers freely by name without giving any supporting textual references; this the present writer has found a little irritating, and so he has adopted the practice of referring to individual workers by name perhaps less frequently but as far as possible giving the specific reference when he does mention a name; repetition has been avoided, as far as possible, so that when a reference is missing the reader should turn to an earlier chapter on a cognate subject. A few classical references are included, but for the most part the references are to recent work. This rather haphazard selection of references has led, the writer finds in retrospect, to his giving prominence to his own work, and to some extent to that of his immediate associates, out of all proportion to its importance, and to his frequently failing to mention the more important work of others, who he hopes will forgive him.

Such references as are given the writer believes are accurate; for checking these references he has to thank Mr. Sur, the librarian of the Calcutta School of Tropical Medicine.

ILLUSTRATIONS

The majority of the figures and illustrations are original; when they have been borrowed from the books or papers of other writers, the reference is given. Wherever possible, the permission of the author has been sought, but in these difficult times, when it may take six months to get a reply to a letter, the writer has in several cases anticipated an affirmative answer; he offers his apologies to these authors. The one or two exceptions to this rule are where charts have been taken from the museum of the Calcutta School of Tropical Medicine, and it has not been possible to trace their source. The original drawings of plates I and II were made by Mr. Roy, the artist at the School, and either he or Mr. Mullick drew the 'cycles' from the writer's very crude sketches; he gratefully acknowledges the assistance given by these two artists.

For the loan of the blocks of some of the illustrations that have appeared in the *Indian Medical Gazette*, the writer's thanks are due to the publishers, Messrs. Thacker, Spink & Co. (1933), Ltd., and for those that appeared in his book, *Kala-Azar*, to the Oxford University Press.

ACKNOWLEDGMENTS

The writer's sincerest thanks are due to Lieut.-Colonel Seward, Officer in charge, Medical Division, 47th British General Hospital, for reading through all the proofs, for pointing out many mistakes that had been overlooked, and for making several valuable suggestions that have now been adopted, to Dr. R. N. Chaudhuri for material help in several chapters and assistance with the proof reading, above all to Dr. Lowe, not only for his contribution, the chapter on leprosy, but for reading through the typescript and making many destructive and constructive criticisms and for seeing the last part of the volume through the last stages of its publication, and to many other colleagues who have helped him in various ways.

The writer's special thanks are due to Brigadier G. Covell, C.I.E., I.M.S., Director of the Malaria Institute of India, and to Dr. R. Kirk of the Sudan Medical Service for going through the final drafts of the malaria and sleeping sickness sections, respectively, for pointing out errors of fact, and for making constructive suggestions. While it was possible to make corrections and to take advantage of the suggestions, it was not possible to send the proofs to these officers for final approval and the writer must assume full responsibility for the correct interpretation of their suggestions.

The writer has to thank Colonel W. S. Robertson, commanding the 47th British General Hospital, for the loan of the skiagrams shown in plates XIII and XIV and for the temperature charts from which figure 135 was copied.

THE TWO PARTS

The writer had—and it can be said still has—no intention of writing a two-volume book; circumstances have however dictated that the book shall appear, at least in the first instance, in two halves. Only part of the edition will be bound, so that when the second half of the book is ready, those who already have the first part may complete their copy, and those who have not may buy the complete book.

The point at which the guillotine fell was determined solely by the writer's departure for the United States; the second part will be about half the size of the present part, and will contain, amongst others, a chapter on yaws, several chapters on tropical ulcerative conditions, helminthic infections, and diet and dietetic diseases, a chapter on anæmias of the tropics, and one on snakes and snake bite. Much of this second part is in an advanced stage of preparation, and, though considerable delay is inevitable, it is hoped that the second volume will appear within the year.

One of the main complications of this division of the book is the index, and, to keep down the cost of the volume, it has been decided to print only a very abbreviated interim index in the first part. The writer feels that this will not be a serious defect, because much of the work of an index has been done by the contents lists at the beginning of each chapter. A full index will be included in the second part.

L. E. NAPIER.

March 20, 1943,
Bombay.

Note concerning the index.—Dr. Napier planned to publish this book complete in one volume with a good index before he left India. The situation which made this impossible is explained above.

Dr. Napier asked me to prepare a brief index for this part pending the completion of the book with part two. On consideration of the

matter (but without Dr. Napier's approval, because of distance) I have decided that anything but a really complete index will be unsatisfactory, and time has not allowed the preparation of this.

I beg the reader's pardon for this omission, which is rendered less serious by the fact that each chapter begins with a detailed list of contents with page numbers ; this is in addition to the ordinary contents page at the beginning of the book. Readers should therefore have little difficulty in tracing the references to any particular subject.

J. LOWE.

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The Genesis of Tropical Medicine.—Present-day scientific medicine was born and nourished through all its earliest stages in temperate western countries. When the people from the western civilizations invaded the East, in a military or a commercial sense or simply as scientific or dilettante travellers, they found that the medicine practised in many of these countries was the crudest form of traditional folk-lore, though in others, such as India and China, there were established systems of medicine which intrigued these western invaders and from which the doctors amongst them gathered some useful recruits to the pharmacopœias of their own countries.

However, early in the nineteenth century, the superiority of scientific medicine over the local traditional systems became obvious, not only to the visitors but also to the indigenous inhabitants of these countries, and more practitioners were demanded. Such large numbers could not be spared from the West, nor could the people of the tropical countries afford to support them in the style in which quite justifiably they demanded, to compensate them for the conditions under which they had to live; medical schools and colleges therefore were founded in the tropical countries to train the natives of these countries in methods of scientific medicine.

About the middle of the last century, it began to dawn on the still conservative mind of the practitioner of scientific medicine in the tropics that, whilst the medicine that he had been taught was very much better than indigenous medicine, as it was then practised, he was frequently encountering syndromes to which there was no reference, or only very misleading references, in his textbooks. Amongst those who had the gift of being able to think ahead of their time and the energy to stir up others to take action with them, Patrick Manson stood out. Many of his predecessors and contemporaries played their several parts, and books on the diseases of various tropical countries were written, but it was Manson who gave this study of tropical diseases a definite form; a new branch of medical science came into being, and rightly Manson is looked upon as the father of tropical medicine. Through his energies the London School of Tropical Medicine was founded and for many years his book stood alone as *the* textbook on tropical diseases.

Nothing succeeds like success, and the early successes in the field of tropical medicine, which may be typified by Ross's work on malaria, stimulated this new branch of medical science, and other schools of tropical medicine were founded in Europe and North America.

From one point of view this awakening of interest in the study of tropical diseases had come too late, for already in certain tropical countries, India in particular, in the medical schools and colleges, to the founding of which reference was made above, western traditions of scientific medicine which took little account of tropical diseases were firmly established. The textbooks used were written by people who had never been in a tropical country and who knew nothing of local conditions and the diseases that they engendered, whilst the curricula and the course of study were faithful copies of those of western schools and universities. The doctor so trained often had a profound textbook knowledge of, shall we say, cardiology and may have been able to spot histological sections of rare sarcomata, yet was quite unable to stain a blood film for malaria parasites or to recognize an amoeba in a stool, and, although he knew that quinine and emetine were specifics used in malaria and dysentery, he had no other ideas on the proper treatment of these diseases which might well constitute 75 per cent of his practice. If he wished to gain special knowledge of how to treat these diseases, he had to go to London, Hamburg, or Baltimore.

The absurdity of this position was appreciated by many, but the remedy was not obvious. The teachers in the schools and colleges, in India at least, were so deeply imbued with the established tradition that it was not possible to call a sudden change, if anyone had had the power to do so; but this power was not vested in any central authority. It was Leonard Rogers, who already had a world-wide reputation for his many researches in tropical medicine, who saw a way out of this impasse, and, with the encouragement and a considerable amount of financial help from the commercial communities and large industries, won over the official opposition and founded the Calcutta School of Tropical Medicine, for post-graduate instruction and research in tropical diseases. He hoped that in time the teaching in this school would have a leavening effect on medical education throughout India, and possibly in other tropical countries, not only in the final years of practical work but in due course in the physiological laboratories and possibly even in the dissecting rooms, and that when it had done its work and outlived its usefulness in this direction this school would remain as a centre of research and higher post-graduate studies.

This is the writer's explanation of the anomaly of a post-graduate school in a tropical country where instruction is given to the local practitioners in subjects which should have been those most emphasized in their qualifying medical course.

Defining the Scope of Tropical Medicine.—The separation of tropical medicine from the body corporate of medical science is thus an artificial, and one hopes only a temporary, one. Nevertheless, at the present day, separate it is and very conveniently separate. The question now arises, is it possible to define its scope? It is certainly difficult. The problem that will exercise the minds of our successors more than it does ours is, how much teaching on the physiology of hot climates should be included in this subject? Our excuse for the comparative neglect of this subject at present is the fact that, as there is so very little accurate information on it, one hesitates to give information that may be misleading; but this state of affairs is changing. The next question is, how far should one go into the subject of tropical hygiene? This brings one to a wider question of medical policy, namely, the past tendency to separate, the present hesitancy, and the future decision (we foretell) to link much more closely prevention and relief in medical education and practice. In his teaching of tropical medicine, the writer has solved this problem by laying special emphasis on the preventive aspects of specific diseases whilst leaving the subject of general hygiene to other lecturers.

What are the diseases that should be included—all diseases that occur in the tropics? This of course is out of the question, as there are few recognized diseases that do not occur in the tropics. Then should it be diseases that only occur in the tropics? This is equally out of the question, for many diseases that are always looked upon as tropical diseases, malaria, cholera, dysentery, also occur in the temperate zones. So we must fall back on an elastic definition and say that under this heading should be included diseases that occur only in tropical and sub-tropical countries, and also diseases that are either more prevalent or else exhibit special features in these countries.

The Changing Picture.—The position is not however static. Many diseases that were at one time world-wide in their distribution are now confined almost entirely to tropical countries; of these perhaps the best example is leprosy. Leprosy was a cosmopolitan disease, common enough in England a few hundred years ago, as is evidenced by the leper windows that still exist in many old churches, but it has now disappeared almost completely from most western countries. Malaria has been banished from England and many other European countries, and yellow fever from the east-coast ports of the United States of America to become a disease with an essentially tropical distribution. Cholera and plague have probably always originated in tropical countries, but in the past have flourished for a time in temperate climates. Epidemic typhus, which on the other hand never had any special liking for tropical climates, and which, since its activities have been largely curtailed in cold climates by improvements in social and sanitary conditions, leads a precarious existence in the sub-tropics; is probably classed amongst tropical diseases only because of its ætiological association with tropical typhus.

It seems possible that tuberculosis is now going the same way as leprosy. The 'white man's plague' has certainly changed its colour preference in America and has shown a steady decrease for nearly a hundred years in Great Britain, but it is rapidly increasing in many tropical countries, just as is cerebro-spinal fever, another respiratorily transmitted disease, in the crowded bazars of the east.

Diseases Uncommon in the Tropics.—There are diseases that are less common in tropical countries, *e.g.* rickets, most streptococcal infections, erysipelas, scarlet fever, and carditis, but they do occur; peptic ulcer is often included in this category but is certainly very common in parts of India. A sterile controversy regarding the occurrence or otherwise of rheumatic carditis in the true tropics has broken out in the medical press from time to time. The champions of the former view made their point many years ago, but are tending to push too far their claims for the frequency of the occurrence of rheumatic carditis; relatively and, almost certainly, actually, it is a far rarer condition in tropical than in most temperate countries.

Then, there are diseases that are *supposed* to be less common in the tropics; these include cancer, but it is very doubtful if this is really uncommon. Statistics are vitiated by the infrequency of post-mortem examinations, by poorer diagnosis and poorer facilities for treating the patients when a diagnosis is made, by a much lower expectation of life so that far fewer people reach the cancer age, and by the fact that the numerous other diseases that occur distract attention from cancer as a public-health problem, except in a few instances where its cause is patent, *e.g.* kangri-burn cancer of Kashmir. Enteric was another example; sixty or seventy years ago, there were many discussions in the medical journals as to why enteric occurred amongst British soldiers in India but never amongst the indigenous inhabitants, until bacteriology came along and taught us to recognize as enteric the slightly modified disease that is very common amongst Indians.

ENVIRONMENT AND THE DISTRIBUTION OF DISEASE

There are of course many facts about the distribution of diseases that are inexplicable in our present state of knowledge regarding the exact ætiology of these diseases, but, now that epidemiological data have been collected over a period of many years, it is possible to indicate some of the factors that determine the distribution of diseases in tropical and in non-tropical climates; these factors can be classed as (a) climatic, (b) telluric, and (c) human.

A. Climatic factors.—Climate is brought about by a combination of solar and terrestrial influences; though it is with the sum-effects of these influences that we are concerned, they must be considered first under a number of different headings:—

(i) **Temperature.**—This cannot be expressed as just hot or cold, for hot climates exhibit wide variations in their temperatures, and these temperatures cannot be given simple numerical expression; there are climates that are hot throughout the year, and others that have a very hot and a very cold season; some countries have a temperature that shows little variation during the twenty-four hours of the day, others one that whilst it is extremely high during the day drops very considerably at night, and yet others that exhibit both these features but at different times of year. To convey a proper idea of the temperature of a locality, a full range of 'normal' data for the whole year should be given, but if it has to be expressed very concisely the best figures to give are the mean of daily means and the mean diurnal ranges for the hottest and for the coldest months of the year.

(ii) **Humidity.**—This is expressed as:—

- (a) absolute humidity in grains of moisture per cubic foot,
- (b) relative humidity, indicating the percentage degree of saturation, 100 per cent being complete saturation at the existing temperature,
- or (c) saturation deficiency, which indicates the drying power of the air, expressed as the difference between the vapour tension at dew point and the actual vapour tension at the time, in millibars.

In one country there are wide differences in the humidities in different localities, from season to season, and at different times of the day; the early morning

humidity, which is the one so often given, is always high and gives a very poor indication of the humidity of a place or a season.

(iii) **Air movements and prevailing winds.**—This is recorded in miles per hour or feet per second, two miles an hour being roughly 3 feet per second. In the matter of wind prevalence, an important factor is usually whether the prevailing wind is from the land or the sea, but there are many other considerations too numerous to indicate here.

(iv) **Sunshine.**—This is recorded as the number of hours of sunshine during the day. This important factor appears to receive more attention in weather reports in temperate and cold climates.*

(v) **Barometric pressure.**—Whilst this is subject to considerable irregular fluctuation, localities of the same altitude above sea-level do not show constant variations that would be likely to affect disease distribution. However the constantly low pressure in high altitudes certainly has an effect on physiology and probably on pathology too.

(vi) **Rainfall.**—This is subject to the widest variations according to the locality and the season, and also from year to year; it is expressed in inches per annum and varies from *nil* to 700.

(vii) **Storminess.**—This is certainly an important factor in the make-up of a climate, both in temperate and tropical zones. Though storminess in temperate zones is associated with respiratory disease and rheumatism, on the whole the balance is in favour of the stormy climates, and Huntington (1924) goes as far as to say that it is the northward shift in the storm belt that has caused the northward and westward shift in the centres of civilization, a view not in keeping with that expressed by the writer (*vide infra*).

A factor associated with this is atmospheric ionization and some medical climatologists attribute much in the balance of health and disease to this. Our knowledge on this subject is at present too vague to allow any helpful discussion on this factor.

B. Telluric factors.—These can be considered under two headings :—

(i) **Natural.**—The physical and chemical nature of the soil, the sub-soil water level, vegetation, etc., and the physiographical configuration of the terrain.

(ii) **Artificial.**—Irrigation and drainage, afforestation and deforestation, the building of cities (that shut out air and hold the heat), etc.

C. Human factors.—These include the density of the population and the degree of urbanization, and industrialization to which they have been subjected, the religious practices (*e.g.* in India, *melas* and pilgrimages tend to spread cholera and dysentery, and ceremonial bathing is largely responsible for maintaining their endemicity) and personal habits of the people (clothing encourages lice and typhus, and protects from fleas and plague), their economic status (poverty is associated with deficiency diseases), the state of civilization (yaws appears to cling to aboriginal tribes) and education of the population, and their educability, the sanitary sense and progress of the population, and the degree of contact with, or isolation from, other populations.

Variations in these climatic, telluric and human factors from place to place will determine the geographical distribution of disease, from year to year their epidemic occurrence, and from season to season their seasonal incidence. Nearly all these factors are interdependent and, as they never act singly, it is seldom possible to judge the effect of one alone—*e.g.* the effect of temperature cannot be considered without taking account of the humidity, which is dependent on rainfall, the nature of the soil, etc., and the effect of sunshine is dependent on the humidity and purity of the atmosphere (industrialization). Finally, the effects of the various factors are not constant in different circumstances—*e.g.* cholera in the Punjab is dependent on high humidity; in Bengal rainfall stops cholera.

* One is reminded of the story, told probably with a thousand geographical variations, of the young Englishman just arrived in Calcutta, who started his career badly by walking into his *burra sahib's* office on a May morning and saying 'Another nice bright morning, Sir'; see p. 13, last paragraph—'furor tropicus'.

CLIMATE AND DISEASE

How do climatic conditions prevalent in the tropics bring about tropical diseases? They act directly and indirectly.

A. Direct effects of climate.—The compensatory mechanisms of the human organisms are so elaborate that the direct effects appear to be remarkably few; this is shown by the fact that the physiology of man living in the tropics is basically the same as that of man living in the arctic zones. There are certain immediate reactions to change to tropical climatic conditions that are rapidly adjusted or compensated. These can be imitated in the laboratory or ward, have in the past been studied frequently, by physiologists, and are now, since the introduction of hyperthermal methods of treatment, receiving the attention of clinicians. At the other end of the scale, time measured in centuries produces certain fundamental changes in the human frame which are of interest to ethnologists, but here one is uncertain whether the effects of climate producing these have not also been indirect, through diet and other environmental factors. Between these extremes there are the results of the subjection for months, for years, and for generations to tropical climates, and it is these that are of special interest to the physician. Beyond the observation and explanation of certain obvious differences between the inhabitants of the temperate and tropical countries, such as that of colour, the subject of tropical physiology has been neglected, and, until this gap in our knowledge is better filled, we shall find our study of the pathological effects handicapped.

The sun's rays.—Fundamentally the cause of the difference between tropical conditions and those of the temperate zones is the fact that the rays of the sun are more direct and therefore, other things being equal, produce their effects with greater intensity in the tropics; it will thus be appropriate first to consider what are the direct effects of these sun's rays on the human body. These effects can be classified according to the different rays which strike the earth, thus :—

Spectral classification		Effects	Angström units	
1. Ultra-violet	..	Biochemical rays	1,000	3,900
2. Violet	..		3,900	4,300
3. Blue	..		4,300	5,000
4. Green	..	Luminous rays	5,000	5,600
5. Yellow	..		5,600	5,900
6. Orange	..		5,900	6,200
7. Red	..	Heat rays	6,200	7,700
8. Infra-red	..		7,700	120,000

We have very little data regarding the relative power of the **ultra-violet rays** in tropical and non-tropical countries, but usually there is less interference with these rays in their passage to the earth's surface in the former and their effect is therefore greater. The ultra-violet rays have a low power of penetration, so that their effects are almost entirely on the skin and subcutaneous tissues. One of the definitely established effects is their action on ergosterol, converting it into vitamin D, in the deeper layers of the skin; this accounts for the extreme rarity of rickets amongst children in tropical countries, except where strict purdah is observed or children are unduly protected from exposure to the sun.

On the skin, the most noticeable effect of the ultra-violet rays is an erythema which comes on two hours after the exposure and reaches its maximum in about six hours; this will vary in its severity and in extreme cases will lead to severe blistering. Repeated irritation by exposure will

lead to chronic changes in the skin (*vide infra*). The wave length that produces this erythema is from 2,800 to 3,100 Å.

The natural pigmentation in the skin of the indigenous inhabitants of the tropics acts as a protection against this effect of the ultra-violet rays, and even amongst the white races the brunette is usually less sensitive than the blonde. The pigmentation that follows repeated exposures to the sunlight is brought about by rays of slightly longer wave length, including the visible rays.

The unhealthy pallor of the skin that is often seen in the European sojourner in the tropics is due to the excessive zeal with which he—or more often she—has protected himself from the beneficial sun's ray, combined with unhealthy living and in many instances disease.

The luminous rays again are usually stronger in the tropics; their powers of penetration are greater than those of the rays of shorter wave length, and they probably have a stimulating effect on the blood and tissues as well as a detrimental effect on parasitic micro-organisms, but our knowledge on this subject is more speculative than precise. Their action on the retina is more certain; in excess they cause headaches, a reduction in visual acuity, a decrease of adaptability to comparative darkness which may become pathological in special circumstances (night-blindness), and other pathological changes in the retina.

However, probably the most important are the heat rays; both the physiological and the pathological effects of the heat rays on the body temperature have been studied in rather more detail than have the physiological effects of the other climatic factors. Before considering the effect of heat rays, one must review the physiology of heat balance.

Heat balance.—Heat is produced by the cellular combustion of foodstuffs. Only some 20 to 25 per cent of this heat is converted into energy and the balance has to be dissipated. If this heat is not dissipated, the body temperature, which in man and other warm-blooded animals is normally maintained at a constant level, will rise, and the physiological processes of the body will be interfered with. To maintain this constant level, there must be a balance between the heat that is produced by the metabolic processes of the body and the heat that is lost to the surroundings. Under tropical conditions, the rate of this heat loss is reduced, and there are times when the process of balancing the heat account is complicated by the fact that certain items that are normally on the debit side are now transferred to the credit side of the account, *i.e.* when the atmospheric temperature is higher than that of the body, and heat is actually absorbed from the environment.

Heat production.—In an average man (whose weight is usually placed at 70 kilogrammes or 154 lbs. though the figure is too high for the individuals of many races, *e.g.* southern Indian, average weight about 120 lbs.), normal body functions produce about 100 calories an hour, at rest; work accelerates heat production and a soldier marching with a pack weighing 65 lbs. will produce 8 calories per minute.

• **Heat loss.**—Heat is lost by radiation, conduction, convection, and evaporation. For practical purposes, the means of heat loss can be considered as '*sensible*' loss, which includes radiation and conduction to surrounding cooler objects, and convection, that is loss to the air in contact with the body surface—this air absorbs heat, moves away, and is replaced by more air, when the process is repeated—and '*latent*' loss, which is achieved by unsaturated air absorbing moisture, from the body surface, from the

sweat that has been secreted by the sweat glands, directly from the blood through the epidermis (Whitehouse, Hancock and Haldane, 1932), and from the lungs; during the process of conversion into vapour this moisture absorbs 0.58 calorie of heat per gramme of water evaporated.

Factors affecting heat loss.—Loss of heat from the body is influenced by the following four environmental conditions, (i) the temperature of the immediate environment, (ii) the humidity of the air, (iii) the movements of the air, and (iv) insulation—mainly clothes.

As the atmospheric temperature rises, the loss of *sensible* heat decreases; when the humidity rises, loss of *latent* heat by evaporation decreases; if there is no movement of air, the air in contact with the body tends to remain stagnant, but with an increase in air movement—in all but extreme circumstances—the rate of both *sensible* and *latent* heat loss is increased; and finally clothes catch the radiated heat and interfere with air movement around the body, holding warm damp air in close contact with it—the thinner and more open-woven the clothes the less will be this interference.

In order to maintain the balance, heat generated must be lost; if it cannot be lost by one means it must be lost by another. At a dry-bulb temperature of 67°F. and a relative humidity of 60 per cent, three-quarters of the heat loss is *sensible* and a quarter *latent*. Under tropical conditions this proportion will not be maintained, and, as the temperature rises, the ratio of *sensible* to *latent* heat loss falls, until eventually when 98.4°F. is reached all the heat loss will be *latent*; after this convection, conduction, and radiation are transferred to the credit side of the heat balance account (though 'debit' as far as the person's comfort and well-being are concerned). The rôles of air-stagnation and clothing are now complicated by the fact that, while reducing loss of *latent* heat, they also limit *sensible* heat absorption (*e.g.* under extreme conditions in desert areas the hot dry winds soon upset the heat balance; hence the heavy *burnouse* of the Arab).

The comfort zone.—The comfort of a man depends on the ease with which he can maintain his body temperature at the correct level; if the loss of heat is too rapid, his peripheral vessels contract and other physiological processes for conserving heat come into action, and he experiences a sensation of cold. Conversely, if the *sensible* heat loss—over which the normal physiological processes of the body have little control—is too slow, other means of heat loss have to be increased, the peripheral vessels dilate and more sweat is secreted, and he feels a sensation of heat. In either case he feels uncomfortable. Man however is a fairly adaptable being and the range of environmental conditions in which he feels comfortable is not very narrow; this range is conveniently known as the 'comfort zone'.

The comfort zone cannot be expressed in terms of temperature, because there are other factors involved, nor of humidity, nor of air movement, for the same reason, but an empirically determined index of the degree of warmth perceived on exposure to different combinations of temperature, humidity and air movement, the '**effective temperature**', has been introduced.

Let us take an example:—at rest in still air with light clothing on a man will find that 75°F. is a fairly comfortable temperature, in the presence of a degree of humidity closely approaching complete saturation, but the same degree of comfort will be experienced at 80°F. in the presence of moderate humidity (60 per cent) and again at 88°F. under very dry conditions (15 per cent relative humidity). If now a fan running at a moderate speed is played on him, he will experience the same degree of comfort in the presence of the three degrees

APPLICABLE TO INHABITANTS OF THE UNITED STATES

F 120

UNDER FOLLOWING CONDITIONS:

Clothing: Customary indoor clothing.

Activity: Sedentary or light muscular work.

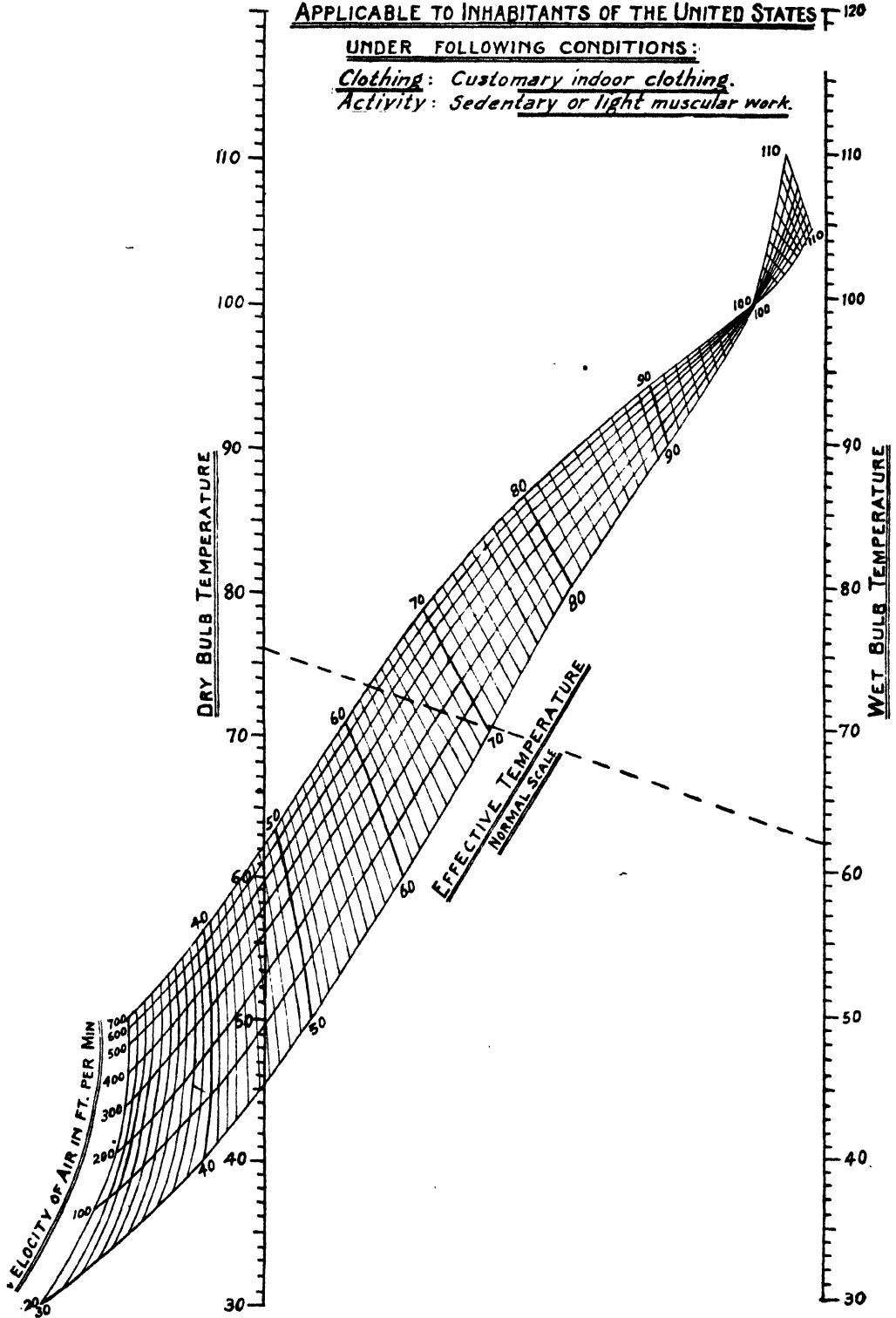


Figure 1

of humidity mentioned above at, respectively, 80°F., 84°F. and 91°F. These six combinations of temperature, humidity, and air movement which produce the same degree of comfort can all be expressed by one figure, namely 75°F. 'effective temperature'.

For calculating this effective temperature a chart is necessary; the chart* given on page 9, from which the effective temperature can be calculated from the dry- and wet-bulb readings and the wind velocity, will be found a very convenient one. (Relative humidity is calculated from the dry- and wet-bulb readings from a chart which is often attached to dry- and wet-bulb thermometers, or from the formulæ and table given below, but this calculation is not an essential step in calculating the effective temperature.)

To calculate the relative humidity from the dry-bulb (DBT) and wet-bulb temperatures (WBT) (after Jameson and Parkinson, 1939)

$$(i) \text{ Vapour pressure (VP) at dew point (DP) = VP at WBT (from table)} \\ - \frac{\text{DBT} - \text{WBT}}{2}$$

$$\therefore \text{ Relative humidity} = \frac{\text{VP at DP (i)} \times 100}{\text{VP at DBT (from table)}}$$

Example. DBT = 75°F. WBT = 67°F.

VP at WBT (from table) = 22.6.

VP at DBT (from table) = 29.7.

$$\therefore (i) \text{ VP at DP} = 22.6 - \frac{75 - 67}{2} = 18.6$$

$$\text{and (ii) Relative humidity} = \frac{18.6 \times 100}{29.7} = 62.62 \text{ or } 63 \text{ per cent.}$$

(Incidentally, the 'effective temperature' in still air with this combination is 71.5°.)

Vapour pressure table (at saturation):—

Temp., °F.	VP in millibars	Temp., °F.	VP in millibars	Temp., °F.	VP in millibars	Temp., °F.	VP in millibars
30	5.6	47	11.0	64	20.4	81	36.1
31	5.8	48	11.4	65	21.1	82	37.3
32	6.1	49	11.8	66	21.8	83	38.6
33	6.4	50	12.3	67	22.6	84	39.8
34	6.6	51	12.8	68	23.4	85	41.1
35	6.9	52	13.2	69	24.2	86	42.4
36	7.2	53	13.7	70	25.1	87	43.8
37	7.5	54	14.2	71	25.9	88	45.2
38	7.8	55	14.8	72	26.8	89	46.7
39	8.1	56	15.3	73	27.7	90	48.2
40	8.4	57	15.9	74	28.7	92	51.3
41	8.7	58	16.5	75	29.7	94	54.6
42	9.1	59	17.1	76	30.7	96	58.0
43	9.4	60	17.7	77	31.7	98	61.7
44	9.9	61	18.3	78	32.8	100	65.5
45	10.2	62	19.0	79	33.9	105	76.0
46	10.6	63	19.7	80	35.0	110	88.0

The comfort zone is thus expressed best in terms of effective temperature, but effective temperature takes into account only three out of the four environmental factors that influence loss of heat, that is, it leaves out of consideration clothes, a factor to which it is difficult to give

* Chart prepared by the American Society of Heating and Ventilation Engineers: *Heating, Ventilation and Air-Conditioning Guide*, 1939.

accurate numerical expression*. The clothes factor and the personal factor tend to widen the range of the comfort zone.

The comfort zone can only be ascertained by actual trial. The subject has been investigated in a number of American cities in winter and in summer, and the peak of the comfort zone has been found to vary between 66° and 72° effective temperature; data for the tropics are still wanting, but one may safely assume that the peak will not be lower than 72° , and, as the zone extends for a few degrees on either side of this peak, 75° , the example that the writer took from personal experience, is probably well within the comfort zone for most tropical climates.

Beyond this comfort zone, there is a zone in which man is definitely uncomfortable, but is still able to maintain his normal temperature. The degree of discomfort experienced will depend on his previous experience and his mental attitude towards the heat; as a rule those more highly educated resent it, whilst others accept it as inevitable. The reactions of man in this 'discomfort zone', as we will call it, will depend very largely on the personal factor and health will play a vitally important part; in some, even quite healthy persons, there will be a very slight rise of the general temperature level; that is, the normal diurnal fluctuations will occur but at a high level. One should not be too ready to jump to the conclusion that this 'low fever' in a patient is physiological, but, if the patient does not suffer any other subjective symptoms and if thorough investigation does not reveal any infection, it may be safe to ignore it; however, should the patient 'feel the fever coming on'—the actual occurrence of fever being confirmed by a tested clinical thermometer—and have a headache and slight shivering, the search for the cause should be continued. In figure 2 the results of different effective temperature levels on the body temperature are shown; the graph was constructed from experience with artificial 'fever therapy' and is probably not applicable to natural conditions. As a general rule there is probably little rise of body temperature below about 90°F . effective temperature, which corresponds to a dry-bulb temperature of 99°F . at 60 per cent, 110°F . at 30 per cent, and 122°F . as 15 per cent relative humidity, in still air, or under the influence of an electric fan, running at a moderate speed, creating an air current of 300 feet per minute, 102°F ., 112°F ., and 123°F ., respectively, at the same three humidities.

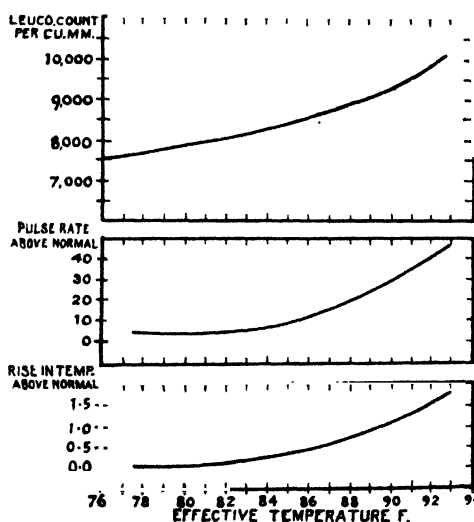


Figure 2: Effects of high environmental temperatures (Ferdcher and Houghten, 1941).

*The intercepting value of clothes is correlated fairly closely with their weight. For example, women's summer clothes (excluding foot-wear) weigh under a pound, men's summer clothes about 3 lbs., and men's indoor winter clothing about 6 lbs. At 50 per cent humidity, comfort will be experienced at 74° , 71° and 66° effective temperatures according to which of these types of clothing is worn. As a rough basis of calculation one can say that an allowance of about 1.6° effective temperature per pound should be made for clothing, excluding foot-wear (Yaglou and Messer, 1941).

Finally, beyond this 'discomfort zone' conditions are encountered under which man cannot survive for any length of time without his temperature rising; the hyperpyrexia and shock that may result from subjection to such conditions must be considered under the heading of 'diseases due directly to climatic conditions' (*vide infra*).

Other Physiological Effects.—Some of the effects of tropical climatic conditions on other body functions and systems can be briefly reviewed.

A change to a tropical climate is accompanied by an increase in **blood volume** (Barcroft and Marshall, 1923), which is apparently a dilution, for the hæmoglobin and other elements show a corresponding relative reduction. This reduction, certainly as far as the formed elements are concerned, is compensated very rapidly, and there is little evidence that the increased blood volume is maintained. Subjection to heat equivalent to that frequently encountered in even moderate tropical climates will lead to a temporary increase in **pulse rate** (*see figure 2*), but the normal pulse rate of the inhabitant and of the sojourner in the tropics (this term is used in reference to those who normally live in a temperate climate but are temporarily living in—not just travelling through—a tropical country) is about 75.

The **blood pressure** of the sojourner is apparently not materially changed by residence in the tropics, though possibly low blood pressures are more frequently encountered than in temperate climates. On the other hand, that of the indigenous inhabitant is distinctly below the European

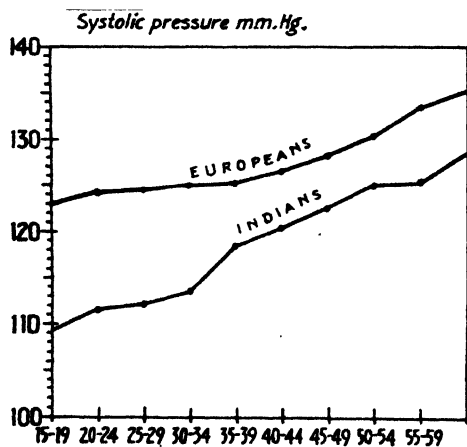


Figure 3 : Blood pressure of different age groups.

and American standards (Cadbury, 1922; Kean, 1941). A recent investigation in which 10,000 Indians were involved showed that the systolic pressure at different ages was from 7 to 10 mm. of Hg. and the diastolic from 5 to 7 mm. of Hg. lower than the European standards at the corresponding age (*see figure 3*). The blood pressure of Indians from the north (the Punjab) was a millimetre or two of mercury higher than that of southern and eastern Indians (from Madras and Bengal). Meat eaters showed pressures 1 to 2 mm. higher than the pure vegetarians.

The **respiration rate**, after acclimatization, is apparently slightly decreased, but the volume of each breath is increased. There is—judged on balance of conflicting evidence—a slight decrease in the normal **basal metabolic rate**, and this corresponds with the lower calorie requirement of the tropical resident.

Subjection to high temperatures is said to depress **hæmopoietic function** (Stokers' anæmia), but recent data on this subject are wanting. The 'thin' blood of the tropical inhabitant is certainly a myth. The normal standards for hæmoglobin amongst healthy Indians, for example, are closer to the American than the British standards (the former being inexplicably higher), and the normal range amongst white sojourners is distinctly higher than even the American standards (Napier and Das Gupta, 1942). The higher

hæmoglobin normals at high altitudes is recognized as a compensatory mechanism and it is probable that a greater oxygen-carrying power of the blood is necessary to counter-balance the lower oxygen tension in the hot air of the tropics.

Moderate heat will cause a rise in the **leucocyte count** (*see figure 2*), but this is apparently not maintained, for the average leucocyte count in tropical residents is certainly not higher than in residents in temperate zones. There is however evidence that the stimulation of the leucopoietic tissue is maintained, for there is a persistent shift to the left in the Arneth count, indicating a more rapid turnover of polymorphonuclear leucocytes, which in many cases is unassociated with infections. There is also a persistently higher eosinophil count, but it is impossible to exclude causes other than the climatic conditions for this.

Endocrine functions are not materially affected by tropical conditions, in health, though there is evidence that in hot monotonous climates certain endocrine organs, especially the adrenal glands, or rather the thyroid-adrenal system, suffer from lack of the frequent stimulation that they enjoy in cooler climates, and consequently fail to rise to the occasion in diseased conditions. There is some effect on the sex glands, for on the whole the inhabitants of the tropics tend to reach sexual maturity earlier, and they are certainly liable to an earlier decline. Mills (1941) takes an opposite view and quotes figures in support, in which he shows that Panamanian and Filipino girls not only reach the menarche later, but that in them the lag between this time and the first conception is far greater than in Negroes living in temperate America. During the ages of maturity, the sex urge is probably less in the true tropics, but in the sub-tropics, where there are wide variations in temperature including the highest temperatures to which man is normally subjected, we have the authority of India's leading sexologist that the 'Arabs of Arabia are the sexual athletes of the world'. The sex urge of the sojourner is popularly supposed to be stimulated on arrival in a tropical country, but it is possible that this is a false impression created by the reduced opportunities for legitimate and the increased opportunities for illicit relief.

The digestive functions—independently of food requirements that are slightly but distinctly lower, especially with reference to fat and protein—do not appear to undergo any great change. The writer and his co-workers, and now also many other observers, have refuted the statement frequently made that the gastric acidity is lower in the tropics; in our experience the normal acid-curve is higher than that given in British and American textbooks. It is certainly true that a hypotonic condition of the gastrointestinal tract is commoner amongst sojourners, especially women, than amongst the same persons living in cool climates, but there is little evidence of this in the local inhabitants, and it is difficult to exclude bowel infections as the cause. The hyperæmia of the skin induced by a hot climate may lead to an ill-distribution of blood and a relative ischæmia of the digestive organs with resultant hypofunction.

The psychological and neurological effects of climate *per se* are hard to estimate on account of the influences of other factors. The nervous irritability, the classical 'furor tropicus', of white sojourners is undoubtedly evidence of their failure to accommodate themselves to local conditions, not necessarily all climatic, for there is no evidence of this in the indigenous population or in the more moderate and more adaptable sojourner. Similarly, there is little evidence that tropical neurasthenia is a direct climatic effect, though here again the monotony of the tropical heat

fails to provide beneficial periodic stimulation. Failure of memory, which is referred to as West Coast memory, Bengal head, etc., according to the locality, though it is common in all tropical countries, is probably more a result of the environment and the circumstances than actual temperature, and may be a manifestation of a mild form of neurasthenia, associated with inability to concentrate. On the other hand, neuralgias are certainly less evident in a hot than in a temperate climate.

There is no evidence that ultra-violet rays of the sun have any direct action on the brain or spinal cord; they do not in fact penetrate even the skin, and certainly not the skull. But the visible rays may have an effect on the retina causing a temporary and in certain cases a permanent reduction in visual acuity, and also night-blindness (*vide supra et infra*); these changes may react constitutionally and produce headaches, vomiting and other symptoms often wrongly attributed to the direct action of the ultra-violet rays on the brain and cord.

The evaporation mechanism of the inhabitant in the tropics is attuned to the local conditions, and their 'invisible' perspiration is much more effective in keeping down body temperature than the profuse and wasteful perspiration of the sojourner; this helps to explain the greater frequency of heat ill-effects in the latter (Lippmann, 1942).

The continuous hyperæmia and moistness of the skin in the tropics probably does not actually produce any pathological change, but it tends towards the blocking of the sweat glands, it allows certain infections to establish themselves more easily, and possibly it prevents others.

Pathological changes.—When the compensatory mechanisms of the body fail, or when the changes brought about by extreme environmental conditions have passed beyond the physiological limits, the conditions produced must be classed as diseases (*vide infra*) caused by the direct effects of climate.

B. Indirect effects of climate.—Whilst the direct effects of tropical climates can be dismissed in 20 pages, the indirect effects form the subject matter for the rest of this book. These indirect effects of a tropical climate are determined by the nature (a) of the food crops that in turn determine the state of nutrition of the population and the specific deficiencies that prevail amongst them, (b) of the bacterial, protozoal and helminthic parasites that are the causal organisms of disease, (c) of the insect life that transmits these causal organisms to man, and/or (d) of the animals that carry or act as reservoirs of infection; or climate acts, (e) by favouring, or the reverse, the natural enemies of insect vectors and animal reservoirs of infection, and (f) by determining the balance of biological competition amongst insects, fish, birds and mammals.

Theoretical.—There is scarcely any limit to the indirectness of the ways in which climate may react on the distribution of a disease, and the important climatic factor may appear at first sight to have as slender a connection with the particular disease as the cow with a crumpled horn had with the house that Jack built. For example, the normal climate in a locality might favour a certain crop that was parasitized by an insect that was the main food supply of a bird that fed alternatively on another insect that was the transmitter of a human disease. A bad year (climatically) might lead to the failure of the crop which one would expect would lead to a dearth of the parasitizing caterpillar, so that the bird would have to turn its attention to the disease-transmitting insect, with the resulting fall in incidence of the human disease.

The effects of climate may thus be not only indirect but very complex and difficult to explain. If, to follow the hypothetical case given above, one wished to explain the decrease of the disease on the climatic factor, it would not be safe to assume any single step in the effects and counter-effects; it would be

essential to ascertain whether unfavourable conditions to the plant did in fact cause a decrease in the caterpillar population, or whether, as often happens, interference in the nutrition of a plant led to an increase in parasitization, whether the birds actually were induced by shortage of their primary food to feed on the disease-carrying insect or whether in fact they were driven away to other feeding grounds, and whether, even in the presence of a surfeit of caterpillars, they did not continue also to take their quota of the disease-carrying insect. Armchair theories on the probable epidemiological effects of certain climatic factors are dangerous and as often as not have to be reversed when actual investigations are carried out.

REFERENCES

- BARCROFT, J., and MARSHALL, E. K. Note on the Effect of External Temperature on the Circulation in Man. *J. Physiol.*, **58**, 145.
- CADBURY, WM. W. (1922) .. The Blood Pressure of Normal Cantonese Students. *Arch. Int. Med.*, **30**, 362.
- FERDERBER, M. B., and HOUGHTEN, F. C. (1941). Effective Temperature Scale. *J. Amer. Med. Assoc.*, **116**, 474.
- HUNTINGTON, E. (1924) .. *Civilization and Climate*. Yale University Press, New Haven.
- JAMESON, W. W., and PARKINSON, G. S. (1939). *A Synopsis of Hygiene*. J. and A. Churchill, Ltd., London.
- KEAN, B. H. (1941) .. Blood Pressure Studies on West Indians and Panamanians living on the Isthmus of Panama. *Arch. Intern. Med.*, **68**, 466.
- LIPPMANN, A. (1942) .. On the Insensible Perspiration and its Clinical Significance. *Med. J. Australia*, **1**, 569.
- MILLS, C. A. (1941) .. The Influence of Climate and Geography on Health. *Bull. New York Academy Med.*, **17**, 922.
- NAPIER, L. EVERARD, and DAS GUPTA, C. R. (1942). *Hæmatological Technique*. Thacker's Press and Directories, Calcutta. Summarized from *Indian J. Med. Res.*, **23**, 305, 311, 973; **24**, 855, 1159; **25**, 529; **26**, 541; **27**, 253, 1009; **28**, 207; **29**, 375, 903.
- WHITEHOUSE, A. G. R., HANCOCK, W., and HALDANE, J. S. (1932). The Osmotic Passage of Water and Gases through the Human Skin. *Proc. Roy. Soc. Med.*, Ser. B. **111**, 412.
- YAGLOU, C. P., and MESSER, A. The Importance of Clothing in Air Conditioning. *J. Amer. Med. Assoc.*, **117**, 1261.

MEASURES FOR MITIGATING THE EFFECTS OF TROPICAL CLIMATE

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Introduction.—The early civilizations were all in warm countries; here primitive man found food plentiful and life comparatively easy, so he had time to turn to the arts. Then, when he learnt to make clothes and build houses, he found that he could overcome the adverse environment of colder climates more easily than that of hot climates; further, it was in the latter, far more than in the former, that his natural enemies—from filterable viruses to tigers—flourished, so he developed an increasing preference for cooler climates, and the centres of civilization tended to drift thither. Now we are learning how to control our environment in hot climates also, and it seems possible that this drift may be stopped, or even reversed.

The history of civilization has been described as the story of man's struggle against his environment. Perhaps, even more appropriately, the maintenance of health, which is the eventual aim of medical science, might be said to be achieved by a process of adaptation of man to his environment on the one hand, and of the environment to man on the other.

Here we are concerned especially with a tropical environment and we have discussed above the ways this may influence the health of man. The effects may be direct or indirect. The major portion of this book is devoted to the indirect effects, to the means by which we can counteract these before they produce diseases, and, when we fail in this, treat the diseases that are produced. In the previous chapter, the direct effects of the tropical environment were discussed; the present one will be devoted to the mitigation of the direct, and in a general way the indirect, effects of the tropical environment by the adaptation of man to this environment and of this environment to man.

The subject will necessarily be considered more from the point of view of the foreigner, as the local inhabitants will already have achieved a degree of adaptation, especially to the more obvious direct effects. Their practices should be studied but never adopted without critical examination as they are quite frequently unsound; further, they are seldom directly applicable to the mode of life to which the foreigner has become habituated for many generations, and partial adoption is often disastrous; our special knowledge regarding the causation of disease must be applied; and, finally, the amenities that recent scientific advances have given us must be superimposed.

Acclimatization.—A very great deal that has been written on the subject of acclimatization has been dependent on analogy and guess-work; in the absence of scientific data the guess-work will have to continue to fill gaps. Lower organisms, individually more susceptible to temperature changes, are by a process of natural selection capable of acclimatizing themselves slowly to changed conditions, but the process takes many generations: in the more complex and more adaptable human individual, the same process will take many more generations, so that racial acclimatization is measured in millenia.

Individual acclimatization is largely a matter of the adaptation of personal habits to the changed environment, but there is evidence that by prolonging the periods of subjection to, and/or increasing the amount of work done in, high temperatures very gradually, it is possible both to increase working efficiency and to obviate the development of pathological heat effects (*see also pp. 39 and 40*). The white sojourner finds the tropical heat very trying because his clothing, the food he eats and drinks, and his general behaviour are less suited to the conditions than are those of the indigenous inhabitant.

What are the usual reactions of the European, who spends the best part of his adult life in a tropical country, to the heat?

The first year he usually finds particularly trying, but he learns how to adapt his habits, and settles down, taking the climate as he finds it, though naturally grumbling in the hottest weather, for the next 15 to 20 years; after this he finds each hot weather more and more trying and the thought of retirement dominates his mind, unless he can get away each summer. There are of course other factors, such as disease and age, but at least the effects of acclimatization are not very apparent.

Again, army statistics for heat trauma show that in the British service the highest incidence is in the young recruit during his first year in India; the incidence then falls rapidly but tends to rise again after about 10 years' service. The figures for heat trauma are lower amongst Indian than amongst British troops under parallel conditions, and this is probably to some extent due to racial acclimatization, but even here other factors,

disease and behaviour, cannot be entirely ignored; heat trauma is seldom uncomplicated and is usually induced by some febrile infection, such as sandfly fever, to which the Indian soldier is more likely to be immune.

The Indian coolie will exhibit his 'pathetic contentment' and not complain of the heat, but it has been the writer's experience that the loudest complaints about the Calcutta hot weather have come, not from his European but from his Indian colleagues. In an investigation on the 'comfort zone' in a bank in Shanghai, it was found that the comfort zone of the Cantonese clerks was lower than that of the European members of the staff.

It will be apparent therefore that the question of acclimatization is not altogether a simple one and that data are urgently required.

INDIVIDUAL HYGIENE

Diet.—The nature of the food taken plays a fundamentally important part in the maintenance of health of the individual and in determining the nature of the diseases from which he is likely to suffer, and in some cases food is the main, if not the only, factor in the production of a specific disease. In investigating a disease in an individual, a rough—if circumstances preclude an accurate—idea of both the food taken recently and the usual diet of the patient must be ascertained, or, in the case of a community, a knowledge of the general diet, and any special deviations that have been associated with the disease, are essential.

The subject of the dietetic requirements of the indigenous inhabitants of the tropics, and of the diseases associated with dietary deficiencies will be discussed elsewhere; here it is proposed to make a brief reference to the dietary requirements of the sojourner. A legitimate criticism might be 'If diet is a matter of such fundamental importance in the maintenance of health in the tropics, why be so brief and so vague?' The writer's reply is that conditions under which the sojourner has to live vary so widely in tropical countries that specific suggestions for one set of conditions would call forth the derision of a majority of readers, that accurate data for even single sets of conditions are rare, and, finally, that this is not a book on dietetics or housewifery.

The dietary requirements in the tropics are distinctly lower than they are in temperate climates. This applies both to the sojourners and to the indigenous inhabitants. A very large number of the latter are vegetarians and though many of the diseases from which they suffer can be attributed directly or indirectly to a deficient diet, which a diet solely vegetable in origin is very liable to be, a well-selected vegetarian diet is certainly better suited to the local conditions than the heavy meat diet that many inhabitants of the temperate climates take.

The sojourner will maintain better health if he reduces his meat meals to one a day. The protein requirements are lower, but if he does not exceed the traditional 100 grammes, further restriction is probably unnecessary; on the other hand, it will be wise to cut down the fat to 70 grammes a day. Fruit should be taken at every meal when fresh fruit is available, and when not, tinned fruit at at least two meals, and as large a variety of vegetables as is obtainable.

The general principles of dietetics should be applied with even greater care in the tropics than elsewhere, because of the abundant infections that are about, ready to attack the individual whose nourishment is not maintained at its peak. Over-eating is probably the deadlier sin, but asceticism is often carried too far.

It is of course essential that all the vitamins should be well represented in the diet. The most common deficiencies are associated with vitamins B complex, C and A, in that order, and iron. In an ordinary mixed European diet and in the ordinary diet of the well-to-do Indian, none of these will be deficient, but there is a danger when invalid diets are prescribed. Thus, to a milk diet, which is the most useful invalid diet in the tropics, fruit juice and marmite should be added and iron given medicinally, and when a fat-free or low-fat diet is recommended some source of concentrated vitamin A, such as halibut-liver oil, must be prescribed.

Constipation is a common complaint amongst sojourners in the tropics, even more so than it is in their own temperate climates; it is enhanced by the dehydration that is likely to occur unless plenty of fluid is taken, and by the tendency of the jaded appetite to encourage the consumption of a high protein diet with little roughage. If the taking of plenty of fluid, fruit, salad, green vegetables, and finally morning porridge fails to make the bowels' action regular, then proprietary bowel 'correctives' such as normacol and isogel, or the more homely agar agar, or ispaghula (*bhusie* obtainable in the Indian bazar) should be tried before one resorts to frank purgatives.

Special care has to be taken not only in the choice of food but also in its preparation and presentation. All fruit and vegetables must be washed with particular care, and any fruit that is to be eaten uncooked should be placed in a bowl of strong permanganate of potash for half an hour, after preliminary washing in clean water, and should then be placed under cover to protect it from flies and dust. Lettuce should be washed leaf by leaf and similarly placed in permanganate. The old dictum 'never eat cut fruit' should be interpreted rationally. It was not based on any evidence regarding the detrimental effect of oxidation, but originated from the fact—at that time probably not recognized—that the cut surface of fruit is a very favourite fly walk, and it need not be applied to the other half of a grape fruit that has been kept, cut side downwards, overnight in an electric refrigerator. Similarly, twice-cooked food, whilst best avoided, as each cooking lowers its vitamin content and usually its digestibility, need not be looked upon as a positive danger in these days of electric refrigerators (by those who use them and use them properly). Water for drinking purposes should always be boiled, and then it is conveniently kept in clean bottles in the refrigerator. There are efficient filters, but most filters are a continual source of anxiety and a dirty or deficient filter is an active danger. (Water supplies and their sterilization are discussed elsewhere.) Milk must be carefully pasteurized or, if this cannot be supervised, it must be boiled.

In most instances in the tropics the servants are natives of the country, or of some other tropical country, their sanitary sense is usually poorly developed, and, even if they observe a strict personal ritual regarding their own food, they do not understand our scientific ritual and cannot be trusted to carry it out. There is, therefore, a wide gap between ordering a thing to be done and either doing it oneself or actually seeing that it is done. The bachelor cannot expect to find time to look after his food in the same way that his wife should do if he had one; he should nevertheless introduce a strict routine procedure regarding the boiling of milk and water and the washing of salads and fruit, so that it can be checked *any* day, even if he does not check it *every* day.

The kitchen, or cook-house, far too often a ramshackle outhouse, is the one room in the establishment over which the greatest sanitary care should

be exercised (*vide infra*). It is not always possible to have a white-tiled kitchen, but a high degree of cleanliness can be attained without this refinement. Above all it should be inspected regularly, and also at odd times, to ensure that the standards are maintained throughout the 24 hours, and it must never be looked upon as the private domain of the servants. If malaria is excluded, probably 90 per cent of the illnesses from which the sojourner suffers are gastro-intestinal in origin and the kitchen is therefore the most important centre whence may radiate good or evil. Yet there are women, looking upon themselves as good mothers and faithful wives, who not only fail to inspect their kitchens daily, but actually boast about this total negligence of their ordinary duties towards their families, often complaining at the same time that they find it difficult to fill their day. When such women come from the classes who in their own countries have a housekeeper and a butler, there is some excuse for them, though they should adjust themselves—as in fact women of this class usually do—to their new conditions, but this is more often the pose of those who never saw a domestic servant in the homes from which they originated.

Another matter closely associated with food is the servants' dusters, tea-cloths, glass-cloths, dish-cloths, etc. Native servants will, if possible, convert anything that is given to them into an all-purpose cloth, which in addition to the above functions will be used for mopping their brows, wiping their noses, straining the soup, and finally, when cold drinks are demanded, for breaking ice in. The potential dangers of such a practice are more obvious than is the remedy, but insistence on the daily exchange of several specific-purpose cloths, each of which should be easily distinguishable, *e.g.* by means of a coloured border, or a check pattern, does at least reduce the concentration of morbid material on each cloth and ensure that at the beginning of each day clean cloths are used.

Much preventable ill-health amongst the sojourner is directly attributable to the 'studied' indolence of their women, and the writer regrets that those of British origin are apparently the worst offenders*.

Beverages and Alcohol

The question of what to drink, which may be an unimportant one in temperate climates, looms very large in a tropical country, because, when evaporation plays such an important part in maintaining a normal body temperature, the physiological requirements of water are much greater. Not only should one's thirst, which is the outward and visible sign of water depletion, be satisfied, but a definite amount of fluid should be taken as a routine; for example, it is a good plan to drink a glass of water on rising in the morning. In hot dry climates, when moisture depletion is considerable, it should be remembered that a considerable amount of salt is also lost in perspiration and that this is not replaced by water, so that it is a good practice to make a habit of taking a tablet of at least 10 grains of sodium chloride with each glass of water.

* This was written in the autumn of 1941. In the first half of 1942, when Calcutta was seriously threatened by invasion, many of these same 'idle' women drove army cars, served in mobile canteens, and generally did a hard day's work in any capacity, without a murmur of complaint, through one of the hottest summers we have had for many years, and at the same time ran their homes with a minimum of servants. It is thus not an inborn idleness, nor, I believe, even a rooted dislike of domesticity, but a stupid tradition that has grown up—in the fostering of which husbands are often by no means blameless—that is responsible for this dangerous neglect of domestic supervision. Dare we hope that the war will kill it?

The greatest obstacle to teetotalism in the tropics is the absence of a 'soft' drink that is really acceptable to the male palate. The 'windy insufficiency' of these is more than an excuse, it is very frequently the reason, for the resort to beer or whiskey and soda to quench an honestly earned thirst. It is of course unnecessary to drink gaseous lemonades or to add soda to sweet drinks, but even drunk 'still' they are very nauseating to many people. There is of course nothing more refreshing than water from a bottle kept in the refrigerator, if the taste of the water has not been spoilt by chlorination. There is also very much to be said for hot tea, at any time of the day, and taken after the day's work its slightly stimulating effect will help to put off the hour when the whiskey bottle is produced. Cold tea properly made can be a very good drink, but probably on the whole cold coffee is more popular. The neat juice of citrous fruits such as oranges, grape fruit, lemons, or limes, which are often abundant and cheap, probably make the best long drinks and are an important source of vitamin C, and tomato juice has been the salvation of many, particularly women, who do not like to refuse to drink, but dislike alcoholic cocktails.

About alcohol, it is not possible to lay down any hard-and-fast rule. The pernicious fable that it is necessary to take alcohol every night 'to ward off fever' is happily dying, but alcohol, taken in strict moderation, in the evening, to ward off depression that often follows the sinking of the sun is a valuable psychological stimulant. For this and other reasons the writer would hesitate to recommend teetotalism to the white sojourner who with his parents before him has probably been used to taking a moderate amount of alcohol, except in the case of one who has already shown instability in this matter, or who has a family history of dipsomania.

On the other hand, to the indigenous inhabitant strong spirits are very often a vice, and though there are many educated natives, Indians, for example, who take a moderate amount of alcohol regularly without any ill-effects, as a rule they seem to be better without it and when they take it are more likely to be immoderate. The peasant in many parts of the tropics takes toddy or some form of native beer regularly without any ill-effects. The same mild indulgence in native alcoholic drinks is common amongst coolies employed in industrial concerns, but in these surroundings they seem more liable to over-indulgence, often to the detriment of their working capacity.

Regarding the safety of drinks taken outside one's own house, it should be remembered that converting water into soda-water does not sterilize it, nor does the addition of alcohol, in the strength in which it is drunk in the ordinary whiskey and soda, make doubtful soda-water safe. Where a drink has to be taken in a strange place, the only safe drink is coconut water, and this is better drunk directly from the shell than from the very doubtfully clean glass that is often offered to one. It is also incidentally as refreshing a drink as any non-alcoholic drink that the writer knows.

Of the alcoholic drinks, whiskey with soda, or better still with water, is the best long drink, and gin and lime juice or bitters, not too 'short', the best cocktail. Mixed cocktails are not to be recommended. Light beer is quite a good drink, but does not suit everybody, and wines do not usually keep well in the tropics, but half a bottle of wine, red or white, with the evening meal, *instead* of spirits earlier in the evening, may be taken without detriment by those who prefer to drink with their meals.

Work and Leave

Western sojourners in tropical countries have brought with them many of their own habits, and amongst these is a restless energy that expresses itself by observing much longer hours of work than the indigenous inhabitants in many countries were previously accustomed to, including working through the heat of the day. There is much to be said against this practice, and, except in large towns where workers live a considerable distance from their work and where therefore a mid-day interval would be of little use to them, it is wise to arrange the working hours in such a way as to take advantage of the comparative cool hours in early morning and evening, leaving a four- or five-hour interval in the middle of the day for rest. The temperature usually reaches its peak between two and three o'clock in the afternoon, so that if a start is made at six o'clock in the morning, six hours of work can be done before mid-day (that is, 2 to 3 hours before the peak is reached) and the rest of the day's work in the comparative cool of the evening.

Whilst a full day's work is certainly not to be discouraged, every opportunity should be taken to get away to a cooler, or at least a different, climate whenever opportunity arises. Many service rules allow the accumulation of leave so that it can be taken at the end of one's service. This is an extremely short-sighted policy from the point of view of the framers, as for the last few years they get the services of a tired rather than a fresh and healthy individual, and it is foolish on the part of the individual to take advantage of it, for his health frequently breaks down and he does not survive to enjoy his accumulated leave. Three-year spells are the longest that a man should be asked to work without 'home' leave in most tropical climates, and as he gets older the intervals between leaves should be shortened. Air travel has made short yearly leave possible and senior sojourners should take advantage of this whenever possible, for the sake of both their bodies and their minds. The longer spells of work should be punctuated by short breaks of even as little as ten days, whenever this can be managed, and the doctor should take every opportunity to order such leave to be taken. It is perhaps part of the mental torpor into which people fall that they are not only indifferent about getting away for a short holiday, but actually oppose the suggestion for no valid reason; this is often because they fear the mental effort of making the necessary arrangements.

Exercise, Rest, and General Habits

Exercise assumes a greater importance in the tropics than in temperate countries. In the latter, even the clerical worker usually finds that walking part of the journey to and from his work, with perhaps a little cycling or gardening at the weekend, is sufficient to maintain himself in reasonable health, though the athletic type may find that he requires a little more than this. In the tropics, although under normal circumstances about the same amount of exercise would probably suffice, there are difficulties in the way of walking to one's work; it is neither pleasant nor healthy to arrive at the office with one's clothes completely saturated, and at the other end of the day, though the same objection does not hold, when one is very tired is not the best time to take exercise, and it takes a certain amount of strength of mind to delay by half an hour the return to the bath and drink that are awaiting. So the sedentary worker usually finds that some form of regular exercise, games or riding, is necessary. These remarks apply equally to the native and to the sojourner, but it is probably on the former that the need for regular exercise requires to be most impressed, for

with the latter exercise is frequently a fetish and is more often overdone than neglected. It is a common fallacy that the early morning exercise expiates the sins of the previous night. Though there are individual variations in the matter of exercise requirements, just as in everything else, it is very largely habit and/or gastronomic and alcoholic excesses that lead to the remark so often heard from the sojourner 'I must have my morning exercise, or I cannot get through my day's work'.

Another fallacy is that increasing weight can be controlled by exercise alone. Figures worth quoting are—that a mile walk will counteract the effects of only two lumps of sugar, a round of golf, one meat course, and five hours of strenuous squash rackets (a physical impossibility) would be required to dissipate the calories acquired at a six-course dinner.

It is very hard to convince the exercise fiend that, if he cut down his nightly whiskeys from eight to two, reduced his evening meal to two courses, and took no exercise in the morning, not only would he feel fitter for his work, but that he would not be nearly so tired at the end of the day, and that his continuous feeling of sub-health is not the fault of the 'blank, blank' climate but of his own habits. The majority of their predecessors died unrepentant (and often prematurely), but the present generation is tending to learn its lesson earlier.

Exercise should be graded according to age—football, hockey, hard singles tennis, and squash rackets are for the young, cricket and mixed tennis can be continued into the forties, after which golf is the game of choice. Riding can be graded to suit all ages, and walking and swimming are always useful alternatives, the last-named being particularly valuable in special conditions such as pregnancy.

As important as exercise is rest. The traditional mid-day siesta is not observed by the majority of sojourners who have their livings to earn, and, except in very hot climates where there is a mid-day break in the daily routine, it has little to recommend it, though for children nearly always, and for women in many circumstances, it is a good practice.

There is probably no single factor more important in the general maintenance of health than a good night's rest, and, as it is difficult to sleep after about 6.30 in the morning in most tropical countries, early retirement to bed is essential (*see p. 30*).

On the whole, smoking is probably more detrimental to health in the tropics than elsewhere. This may be because cigarettes and cheroots are the more common media than the less detrimental pipe. Idle and neurotic women are particularly liable to become 'chain smokers'. It is more frequently on account of gastric disturbances than the toxic action on the heart that one has to recommend abstinence from this practice. There are in the writer's experience far more non-smokers amongst sojourners in the tropics than amongst the same class of individual in their own countries; the reason for this may be medical or otherwise. It is scarcely necessary to contradict another fable, namely that cigarette smoke has any antiseptic value in the case of an air-borne or droplet infection.

Finally, advice on personal habits can be summed up in the simple council—admittedly one of perfection—moderation in all things.

Clothing

In the matter of clothing, it is probable that we can add little to time-honoured local practice; the very scanty clothing of the South Indian coolie and the light loose clothing, easily thrown off the shoulder, of Indians of the educated classes are eminently suited to the hot damp

climate of southern and eastern India, just as the *burnouse* of the Arab is to the much greater but dry heat of the desert. The 'actinic-ray-proof' red lining of the khaki coat is just trade propaganda to sell an article ill-adapted to most tropical conditions.

The pictures of heroic scenes during the Indian Mutiny fill the present-day observer with horror, not an account of the atrocities that were practised by the rebels, but because of the cruelties inflicted on the British soldier by the army authorities who prescribed his broadcloth uniform. The khaki drill that replaced this was a distinct advance, but it seems to have taken the present war to break down old traditions and allow the adoption of the sane and sanitary, but one must admit slovenly, dress of the soldier of 1940.

The civilian sojourner in the tropical metropolis is following this example rather slowly, as individual conservatism is harder to break down than official conservatism in a matter of this kind, but one hopes that the 'bush shirt' or some other form of open-necked short-sleeved garment will be the accepted 'office wear' before many more hot weathers have been endured.

The essential features are that clothing should be light in colour, so that it reflects the maximum and absorbs the minimum of heat, light in texture and open woven, so that moisture-laden air is continuously carried away from the body and replaced by drier if not cooler air, and light in weight and loosely fitting, so that it does not weigh heavily on the shoulders, and hips, or cling round the neck, legs and wrists, but, again, allows free circulation of air and thereby evaporation.

It is not possible to lay down any hard-and-fast rules for Europeans' clothing in the tropics, as conditions as well as customs vary so widely. For general comfort and efficiency, where appearance and convention may be ignored, shorts and a shirt open at the neck (preferably white but light khaki is more serviceable), the former made of a light drill and the latter of light longcloth or an open-woven cotton material, will be the best; under this a very fine cotton vest and a pair of short trunks, of the kind that give some support to the scrotum, add to the comfort without adding much to the weight.

In the ordinary way, the shorts should be cut to rest on the hips, so that a belt is unnecessary, but for those who have no hips, and in extremely hot damp climates where any constriction round the waist may be intolerable, the shorts can be made to button to the shirt. The disadvantage of such clothing is that it exposes a large area of skin to the sun, and those who are not habituated to the tropical sun should be careful at first; further, this type of clothing leaves a large surface for ticks, leeches, etc., to adhere to, and for mosquitoes to bite at night. In climates where the nights are cool—this applies particularly to dry climates such as that of Egypt—the dangers of both local and general chilling are obvious, and arrangements should be made to change or supplement the clothing towards evening, but the habit of putting on a thick sweater or a heavy coat immediately after a game of tennis, when the wet-bulb temperature is 80°F. and the chances of chilling are very slight, is both unthinking and unhealthy; it is far wiser to allow one's body temperature, which will probably be raised two or three degrees, to return to normal before putting on a wrap.

The flannel **cholera belt**, whose powers of cholera prevention were of course mythical but which could be guaranteed to produce a nice band of prickly heat in most climates, has fortunately gone out of fashion.

Quiescent abdominal infections are sometimes stimulated into activity by local chilling which the cholera belt was designed to obviate; it is therefore advisable for those subject to attacks of diarrhoea to put their wraps round their abdomens, rather than over their shoulders, when cooling off after exercise.

Long stockings that were at one time nearly always worn with shorts are now often replaced by very short socks that do not come above the ankle, or ordinary socks rolled to the ankle; these should be of cotton or silk: Women seldom wear stockings in these days.

'In the Malay States, they have hats like plates which the Britisher won't wear', sang the satirist; nevertheless, we have probably made some advance in the matter of suitable **headgear** and in most instances have improved on the local customs, though even in this there is a great deal of pseudo-scientific nonsense written and talked by the 'trade'. The essential features of suitable headgear is that the brim should be wide enough—at least 5 inches—to shade the eyes and the back of the neck, be light in weight and colour, be held well away from the head, both at the brim and over the vault—air is an excellent insulator—and be well ventilated by generous openings to ensure free interchange of air. These features are not incompatible with a headgear of reasonably æsthetic appearance from the point of view of male fashions, and a fantastic shape is no guarantee of a scientific conception.

European women are recommended to adopt the 'severe' male style and not to attempt to disguise a pith foundation as a recent fashion model; the attempt is always a ludicrous failure.

White is again the best colour and khaki the most serviceable. Pith is the best material, mainly on account of its lightness; the tougher composition of the service and the polo helmets gives added protection in the case of a fall, but not against the sun's rays, and is much heavier. Lining the helmet with aluminium foil is of little practical advantage. The protection given by an ordinary felt hat, and certainly that given by the 'double Terai' with a wide brim, is in most cases adequate from the point of view of interrupting the sun's rays, but neither is so well ventilated as the pith 'topee'.

The protection of the eyes is more important than that of the head, and an experienced tropical sojourner will often wear an eye shade or dark glasses and dispense with headgear altogether (the writer plays golf at any time of year in Calcutta without any head protection), but it is not a practice that one would recommend a recent arrival in the tropics to adopt, until he is more certain of his personal factor. Calobar-D or other tinted glasses are more suitable than really dark glasses in most circumstances, but here again the local conditions and the personal factor are all-important; many people will manage without any glasses in the green tropics, *e.g.* Malaya and Assam, but it would be unwise for anyone to go to Egypt or Iraq without adequate glare-glasses. The reflection from water can also produce very severe headaches.

Footwear again will depend on the circumstances. It would be inadvisable to advocate canvas shoes for tramping through excreta-contaminated soil on tea estates, but for town wear they are far better than leather, in that they allow freer ventilation; 'co-respondent' shoes, made with white canvas in the place of buckskin, are smart enough for town wear and are an excellent prophylactic against 'foot-rot', *i.e.* tinea infection with septic complications (*vide infra*). 'Mosquito boots', with

high canvas tops, are useful for protection in the evenings in mosquito-ridden localities.

HOUSING AND SANITATION

Much can be done to mitigate the ill-effects of the tropical climate by suitable housing. The design of a building will naturally depend on the purpose for which it is to be used, as well as on economic considerations, but, even with regard to the living quarters of the average sojourner and the well-to-do indigenous inhabitant, the requirements will of course vary considerably and depend on the nature of the climate and on other local considerations; on whether it is a hot dry climate or a hot damp climate, and whether in the latter case the rainfall is so high and the drainage of the soil so poor that it will be necessary to have the house raised off the ground, or, in extreme cases where flooding is common, built on high stilts, or conversely whether the damp rising from the ground into the walls of the house will be welcome as an aid to temperature reduction during the hottest time of the year; again whether the walls should be thick and the house built so that it can be hermetically sealed during the hottest parts of the day (as for dry climates), or whether it should be constructed so that the maximum fresh air will be available throughout the 24 hours; whether it should be built to withstand heavy rainfall, or if this is so rare that no allowance need to be made for it; whether it is to be in a town or in the open country; whether it will be necessary to make the building mosquito-proof, or not; whether its rooms are to be artificially cooled, or whether cooling will have to depend on natural methods; and so on.

It will be obvious that the subject of housing in the tropics is a very complicated one. It has seldom been studied scientifically, except as a purely local problem to meet immediate requirements and is still almost entirely in the hands of the amateur, and often not a very intelligent one at that.

When looking at an old house built a hundred or more years ago, in India for example, one often hears the sigh 'Ah, they knew how to build houses in those days'. They did in fact use common sense and build houses with very thick walls and roofs, and high ceilings, and usually with broad verandahs to act as extra buffers between the external heat and the large inner rooms, but today we cannot afford to imitate them even if we wished to do so. The modern builder has tried to adapt himself to changed circumstances, and if he has not been very successful he has the excuse that science has provided him with very few data applicable to tropical climates. Since modern tropical institutes are tending to include chairs of sanitary engineering*, one hopes that the subject will now be studied more thoroughly, and that future writers on tropical medicine and hygiene will not have to depend entirely on the few crumbs of scientific investigation, such as that of Crowden, the importance of which they have to exaggerate in order to disguise the poverty of the meal that they are giving to their readers.

Present-day trends.—The general tendency today is to build the walls of the houses less thick than formerly, primarily because of increased cost, but the thinner walls, if insulated with the low-heat-transmission material, have certain definite advantages over the old type of building with very thick walls.

* Mr. B. Dyer, professor of sanitary engineering, All-India Institute of Hygiene and Public Health, Calcutta, has kindly supplied some of the data given below.

In the old houses, with walls 3 feet thick, built of low-density brick and plastered inside, with a difference of 10°F. between the indoor and outdoor temperature, there was a heat transmission of 1.26 BTU* per hour. With a 12-inch wall of the same type of brick and 1 inch of insulating material, such as Celotex, and the same conditions as above, the heat transmission would be 1.60 BTU per hour, but, with a wall 18 inches thick with 1 inch of insulation, the heat transmission would be 1.30 BTU per hour. There are obvious advantages in thinner walls, if the insulation is equally good; not the least of these is that they are dryer.

The walls should have a damp course of slate, if possible, or otherwise of at least half an inch of neat cement to prevent moisture creeping up the wall. This must be placed below the level of the floor, in order to protect that also. This is specially necessary in India, where in many cases the bricks are poorly burnt and the mortar is of lime and sand, with too great a proportion of sand.

The best roofing, from the point of view of heat deflection, is thatch, the thicker the better, but it has certain disadvantages, in that it makes an excellent harbourage for rats, birds, snakes, and insects of many kinds, and it is easily fired and has to be repaired very frequently. Rats and birds can be kept out by suitable wire-netting.

Pitched roofs are usually of tiles, a composition asbestos material, or galvanized iron, and flat roofs are of brick and concrete. The galvanized iron roof which is cheap and serviceable is not as hot as one would imagine, provided it is painted white and there is a false roof of Celotex, or some other efficient insulating material, to intercept the radiated heat. Celotex is also used in conjunction with concrete, but brick rubble on top of concrete is also very efficient.

A pitched one-inch tile roof with a plastered ceiling has a transmission coefficient of 0.34 BTU per square foot per hour per degree F.; that of a two-inch flat concrete roof with a ceiling is 0.82 BTU; that of a four-inch concrete roof is 0.72 BTU; and that of one with 4 inches of concrete with 1 inch insulation is 0.23 BTU. A corrugated iron roof with no wooden lining has a transmission coefficient of 1.5 BTU, with a wooden lining one of 0.95 BTU, and with 1 inch of insulation a coefficient of 0.25 BTU. A roof of 6 inches of concrete under 9 inches of brick rubble gives a transmission coefficient of 0.337 BTU.

A pitched roof should overhang the walls of the building by at least two and a half feet to protect them from the sun's rays, and also in order to carry the storm water well away from the walls into a properly-sloped drain. Flat-roofed houses, with no overhanging roof, usually have a cornice of about 2 feet over the windows, which reduces the glare, keeps the rain away from the windows, and shades the walls from the vertical rays of the sun.

The roofing material that has been introduced by Crowden, referred to above, consists of three layers, the important layer being the centre one; this consists of a quarter of an inch of thickness of some composition material, the actual nature of which is not important, covered on either side by a very thin layer of aluminium or aluminium foil. The nature of the outer and the inner layers is again unimportant and they will obviously vary with the requirements, but they must be of some non-conducting material and be held at least half an inch away from the centre layer. The efficiency of this roofing in deflecting heat, in proportion to its thickness which need not be more than about 2 inches, is very considerable, but at present its expense precludes it from general use as a domestic roofing, though it is possible that in the golden future when we have turned our swords into plough-shares and our aeroplane scrap into aluminium foil, it may find a wider application. The coefficient of transmission of this

* BTU = British thermal units.

roofing is in the neighbourhood of 0.23 BTU per hour per square foot for each degree of difference of temperature between the inside and outside temperatures.

Floors should be of finished concrete, terrazza or one of the new materials which are so attractive and, having a smooth finish, take a high polish. All the corners, and the angles between the walls and the floor should be rounded to permit easy cleaning.

Ground floors should be at least 18 inches above the ground, and there should be sufficient grated openings on all sides to provide cross-ventilation for the space below the floor.

The ventilation space below the floor has the disadvantage of forming a harbourage for reptiles, rodents, and other animals, and it is a continual source of expense to keep the grating or wiring in a proper state of repair. For this reason a solid plinth is favoured in some places; this must be covered by good concrete to prevent the damp rising up into the house.

Ceilings should be at least 14 feet high; the advantage gained by the extremely high ceilings is not proportionate to the added expense. If the room, or house, is to be air-conditioned much lower ceilings are advisable. A ceiling of 9 feet is not oppressively low, and it reduces the cubic capacity of the room considerably and thereby increases the effect of the air-conditioning.

Windows should be of the casement type, and, if no shutters are provided, should swing outwards. It is a great mistake to have windows too small. They should be $2\frac{1}{2}$ feet wide and 5 feet high, but, even more important than their size is the placing of the windows; they should usually be placed in such a position that cross-ventilation is possible, and advantage can be taken of the varying prevailing winds during the hot seasons. In the tropics, there is some doubt whether the accepted ratio of 1 to 7 window space to floor space applies, as windows must be protected during the heat of the day; the ratio of 1 to 10 with cross-ventilation is more satisfactory.

Good wooden shutters with fixed slats are a great help in keeping down the temperature of the room, and can be used with the glass windows open or closed, according to whether the air is to be shut out or free ventilation encouraged.

Doors should be wide; outside doors should have lintels and also be placed to assist cross-ventilation.

Screening of doors and windows should be done in all malarious countries, whether other anti-malarial measures are adopted or not. The old belief that screening raises the temperature of the room considerably is not borne out by the observations made by many investigators, though it does diminish air circulation. In the Punjab, rented flats must be screened by the landlords, as are government bungalows. The wire-netting should not be coarser than 16 meshes to the inch, in order to exclude mosquitoes (*see also Malaria*).

The **verandahs** should be at least 12 feet wide and of sufficient length to be comfortable; there is a great advantage, in a country bungalow where space is unimportant, in having a verandah all round the house to protect the room walls from the sun, but in a town where space is necessarily limited, when the verandah is to be occupied much during the day, it should face east or north.

The **aspect** of the house is an important point, but no hard-and-fast rule can be laid down. The full range of local seasonal conditions must be considered. In Calcutta, for example, the prevailing wind in the hot

weather is from the south, in the cool weather when the wind may be too cold it is usually from the north, and storms usually come from the north-west, so that, despite the disadvantage of the hot sun during the middle of the day, the south is the aspect of choice.

The **rooms** should be of good size, at least 15 feet square or its equivalent. For country bungalows much larger rooms are the rule and are to be recommended provided air-conditioning is not to be installed, but, if it is, there is a great advantage in a small room, which will usually be sufficient for ordinary living rooms or bedrooms, when properly arranged. For example, wardrobes and cupboards (almirahs) are unsightly and are favourite nesting places of mice, etc. Built-in cupboards are more convenient and save space; the old claim that they are damp is not applicable to modern building construction and has been found to be untrue in many tropical countries.

The **kitchen**, or cook-house, should have a considerable amount of thought devoted to it; it should be in, adjoining, or very close to the main structure, so that it can be kept under the strict supervision of the housewife, and should not be relegated to the servants' quarters, where it is impossible to control it. It should be small, 10 by 12 feet, so that it can easily be kept tidy and will not be used for purposes other than that for which it was designed; it should be well ventilated and as well lighted as any workshop; the floor should be finished with smooth concrete, the walls and ceiling should be of hard plaster, preferably painted white, so that they can be cleaned easily; and the kitchen should be fly-proof.

The excuse for the distant cook-house is that the smell of cooking is offensive; but it is possible to arrange that there is no direct closed communication between the kitchen and the rest of the house, even when it is in or adjoining the main building, and if the servants are made to do their own cooking—the smell of which can admittedly be very offensive—in their quarters, this objection is largely removed.

Bathroom and toilet.—It is usual in the houses of sojourners in hot countries to have at least one bathroom attached to each bedroom, and, as in the hottest weather two or three baths are often taken during the day, it is worth while having the bathroom as large as possible, and fitted with a fixed bath and hand basin and a sufficient number of convenient shelves. A shower and an electric fan are comfortable additions. The floors should be made of polished concrete, which should extend 5 feet at least up the walls, the rest of the walls and the ceiling being painted.

If the spaces under the basin and bath cannot be completely enclosed in concrete, or some other vermin-proof material, it is better to have them altogether open, as the space is always damp and therefore an ideal refuge for cockroaches, centipedes, rats, or even snakes.

It is usual to have a flush toilet pan or commode in the bathroom; it is a convenient arrangement where the ratio one bathroom per person can be maintained, but otherwise it has obvious objections.

Where water is available without 'main' drainage, some form of small septic tank into which the toilet pan can be flushed directly should be built. This is not expensive, but it must be emptied regularly, about once a year, and the effluent has to be arranged for; a bore-hole soakage pit will suffice.

When there is no connected water supply and drainage, a commode with an enamel-ware pan is usually used in India, but this necessitates the continuous services of a 'sweeper' which may not always be possible. The larger type of bucket latrine with an automatic ash sprinkling arrangement,

or simply a box of ashes and a shovel, has very great advantages over the shallow enamel-ware pan where service is irregular, and is popular in many tropical countries.

For garden use, the bore-hole latrine with a light superstructure that can be moved biennially is very satisfactory in most soils, and has the advantage of being cheap. (For 'rural water supplies and sanitation' see other sections.)

ARTIFICIAL COOLING

In a dry climate, use should be made of the *khus-khus tattī*. This is a screen of loosely woven coconut fibre that is hung across a doorway or over a window opening; it is kept continually saturated with water by some automatic feeding device or by hand with the help of a garden hose. The dry air comes in contact with this damp screen and causes evaporation, which absorbs the heat from inside the room. This arrangement can be made more efficient by the use of a suction fan to draw the air through the screen. It is a surprising fact that this does not tend to make the atmosphere of an occupied room moister than when it is just closed up in the ordinary way, but it makes it a number of degrees cooler.

Air-conditioning in offices and houses.—Twenty-two years ago, when the School of Tropical Medicine was opened in Calcutta, one of the largest cities in the tropics, our 'cool' room was one of our most popular exhibits. It was an extravagance that was only justified by the fact that a large freezing plant had to be maintained for storing and preserving sera, etc., and that the cool room was necessary for certain chemical and bacteriological experiments. Its existence was dependent on the foresight of Sir John Megaw, who seven years earlier, before the 1914 war, had seen the necessity for, and designed, this room, and it was appropriate that he, the first director of the School, should be the one to make the most use of it. Gloomy prophets foretold that the users would be victims of all the worst ills that, in a tropical country, chilling is popularly supposed to generate, quite forgetting that in temperate and cold countries people are subjected to many-fold greater temperature changes every time they enter or leave their heated houses or rooms. These ill-forebodings did not materialize, and today our prize exhibit of 1920 is of little interest to visitors of 1942, many of whom have similar installations in their offices and houses, and we are compelled to stress the historical interest as an excuse for showing it at all.

Air-conditioning, which has now been extensively adopted and, had it not been for the present war, would probably have been as commonplace as the electrical refrigerator is today—though possibly restricted to slightly higher economic classes on account of the higher cost—has entirely changed the outlook of many less robust tropical sojourners. With an air-conditioning machine in their bedrooms, they are ensured a cool, quiet and undisturbed night, for not unimportant though secondary advantages of an air-conditioned room are that noise and disease-carrying and other flying insects with a high nuisance value are excluded, and that the light can be shut out far more effectively than when one has to rely on open windows and doors for ventilation.

The principle of the cool room at the School is a very simple one; air is driven over frozen pipes and conveyed by an insulated shaft to inlet holes near the roof on one side of the room, and on the other are a number of openings connected with an exit shaft. The cool and dry air (dried by the precipitation of the moisture when it is cooled) falls in a cascade into the room, and lifts the warm air, which passes out by the air-exit shaft. The walls of the room are lined with an insulating material and covered by glazed tiles, the windows are

double, and the door is a thick one with rubber bands to ensure hermetical sealing; these latter refinements undoubtedly added to the efficiency of the room, but time has shown that they were unnecessary elaborations for the range of temperature that is required.

Today air-conditioning is altogether a much simpler affair; single units are available that can be fitted into any window—in a matter of few minutes if the window is of the sash variety, and after some adjustment if it is a casement window. If the windows and doors are reasonably close-fitting, no special measures need be taken, but, when the building is an old one, the openings that will usually be found around the doors can easily be filled with felt, and, if a curtain is hung over the door, there will be very little interchange of air whenever the door is opened.

The domestic units are designed to cool rooms of different cubic capacities; a machine of about one horse power will usually cool a room of 4,000 cubic feet very efficiently. When the room has a very high ceiling, as is usual in better-class houses in tropical countries even today, it may be advisable to put in a false ceiling, but it should be noted that the 'dead space' at the top of a room is not such an important matter in practice, as one might suppose; though the temperature in this dead space is often 3 or 4 degrees higher than that in the lower part of the room, this fact is not of much importance as this air does not come in contact with the body. Thus, in a high-ceilinged room the cooling will be more efficient than in a low-ceilinged one of the same *cubic capacity*; on the other hand, cooling will be more efficient in the low-ceilinged room than in the high-ceilinged one with the same *floor space*.

For air-conditioning, the best room is one with a north aspect (in the northern hemisphere), with the minimum of doors and windows, and with not more than one outside wall. It is not usually necessary to provide an air exit, but, if this is provided, it should be near the ceiling, or at least above the door height. The air will find some means of escape and if the pressure is on the *plus* side inside the room, this will ensure that the air is passing through such cracks as exist, in one direction only, that is outwards. Where the air in the room is likely to become smoke-laden or otherwise obnoxious, an exhaust fan may be advisable, if this is not already provided in the air-conditioning unit; it is not however advisable to use this exhaust fan unnecessarily, for it always has the effect of raising the temperature of the room, by lowering the pressure and drawing hot air in from outside. The room should have as little furniture as possible in it, as, until every object in the room has been cooled to the air temperature, every surface is giving off heat that has to be absorbed.

The cost of domestic air-conditioning units is not prohibitive; before the present war a machine sufficient to cool a moderate-sized room of about 3,000 cubic feet cost about £100*, and, where reasonably priced 'power' electric current is available, about a penny an hour to run. For the average tropical sojourner, this is not a high price to pay for the very great benefits to health and efficiency that it provides, or, to put it another way, it is better value to have a good night's rest than an extra whiskey and soda.

For those who can afford slightly larger plants and are prepared to make structural alterations in their houses, it is possible to air-condition three or four rooms in a house at a cost equal to that of

* This was the price of a $\frac{3}{4}$ 'ton' ($= \frac{3}{4}$ horse power) machine delivered in Calcutta. In the United States the price was about half this figure.

two individual plants, especially if all the rooms are not likely to be used at the same time.

Commercial houses that have introduced air-conditioning into their city offices have taken this step not as a luxury for their staff but as a sound business proposition.

The temperature that it will be possible to provide in an air-conditioned room will naturally depend both on the machine and on the temperature and humidity outside. The comfort zone in a tropical country, where one is wearing thin clothes, is between 72° and 78°F. with the humidity at 60 per cent, which correspond to 68.5° and 73.5° effective temperatures, respectively, and most efficient air-conditioning plants will usually achieve the latter temperature and humidity even in the most unfavourable weather, but even a temperature of 80°F. with this degree of humidity (effective temperature 75°) will be sufficiently low to ensure a good night's rest for most people.

Most one-room plants will bring the temperature down to very near the minimum level within an hour, and the more powerful house plants, when they are turned on to one room, in a matter of a few minutes, so that it is not necessary to run a plant continuously.

Air-conditioning in operating theatres.—Air-conditioning of operating theatres has been practised for half a century in some large hospitals in England, but during the last few years considerable progress has been made in this subject, especially in America. In addition to the application of air-conditioning to these, maternity and delivery rooms, x-ray rooms nurseries, etc., are being extensively air-conditioned in some countries, but the widest application is still for operating theatres. Complete air-conditioning for operating theatres is desirable even in temperate countries to reduce the risk of explosion of modern anæsthetic gases and for other reasons, but, in a hot climate, for the comfort of the operating personnel, to increase their efficiency, and to reduce the chances of sepsis, it is almost a necessity.

There is still much to be learnt about the patient's temperature requirements before, during and after operation, but some data, especially with reference to fatalities, have been collected, and, although it is clear that the comfortable air conditions for the operator are not identical with those optimal for the patient, a compromise has finally been reached in a relative humidity of 55 to 66 per cent and a temperature of 80°F. in warm weather and about 75° in cold weather.

In 1940, as a result of extensive experiments in the United States, one hospital was rebuilt with the operating theatres completely air-conditioned, by means of two separate air-conditioning systems. One system serves all operating theatres using 100 per cent fresh air which is passed through disinfecting filters before being delivered into the room; the second system, which is a separate one for each operating room, takes care of the fluctuation in the internal load and removes the excess humidity. The final design called for a relative humidity of 66 per cent and a temperature of 80°F. The second system is not used unless needed, but is always ready to meet special circumstances, dependent upon the class of operation being conducted.

DISEASES DUE TO THE DIRECT EFFECTS OF A TROPICAL CLIMATE

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Introduction.—When in extreme climatic conditions, other environmental conditions being optimal, the compensatory mechanisms of the healthy body fail to maintain the body within the normal physiological limits, climate may be considered to be the *sole* factor in the production of pathological changes. More usually however these same pathological changes are brought about by less extreme climatic conditions acting in conjunction with other suboptimal environmental conditions, and/or on a body in subnormal health; in these circumstances climate is only *one* of two or more factors that, acting in conjunction, determine the pathological state.

Under this heading only pathological conditions that are *solely* or *mainly* due to climatic conditions will be included, but it must be remembered that other factors, *e.g.* a specific infection, may influence the symptomatology to a greater or lesser degree, and it will be convenient to consider also in this chapter conditions of multiple ætiology that are sometimes attributed to the climate.

PATHOLOGICAL CONDITIONS PRODUCED BY THE HEAT RAYS OF THE SUN

The following clinical conditions are recognized as being produced by heat :—

- A. *Heat stroke.*
 - (i) *Heat hyperpyrexia.*
 - (ii) *Heat shock.*
- B. *Heat exhaustion.*
- C. *Heat cramps.*

It would perhaps be appropriate to make some remark about the term 'sunstroke' which was commonly used until recently and which still causes a considerable amount of confusion, not only in the lay mind but amongst less well-informed medical personnel. The term was introduced when it was thought that the solar spectrum contained some mysterious ray, usually attributed to the ultra-violet end of the spectrum, that had a direct and detrimental effect on nerve tissue. There is no evidence for the existence of such a ray.

Another objection to the term is the fact that *coup de soleil* (literally 'stroke of the sun') has already been claimed by the French, for quite a different condition, namely for what we know as solar dermatitis. It has been shown that the clinical conditions indicated by the term 'sunstroke' are all produced by heat effect on the body as a whole, though it is conceivable that localized heat applied to the brain or spinal cord might produce parallel conditions.

A. Heat Stroke

Definitions.—*Heat hyperpyrexia* may be defined as a condition in which, in excessive heat, the heat regulating mechanisms of the body fail to keep the temperature below the upper physiological limit. *Heat shock* is another phase of the same condition, in which shock is the predominant feature. The expression *heat stroke* may be used conveniently as a general term to include both conditions.

Epidemiology

Geographical incidence.—The condition is not by any means confined to the tropics, nor is it even more common in the tropics. The heat stroke incidence in the hottest months of the year in Calcutta and Singapore is

lower than it is in a heat wave in New York; during heat waves in American cities the deaths attributable to heat amount to thousands per week. In the latter cities, the other environmental factors, both personal and general, that is, the unsuitable clothes, housing conditions, etc., enhance the effects of the climate on an unacclimatized population. Again, it is in the dry desert areas of North Africa, Arabia, Iraq, Iran and the North West Frontier of India that the condition is more frequently encountered than in the true tropics.

Seasonal incidence.—It is of course in the hottest months of the year that most cases occur, and army statistics in India show that all heat hyperpyrexia occurs between May and September, half the cases occurring in June.

Sex, race, habitus, and habits.—Male adults form the bulk of the victims, mainly on account of the circumstances under which they have to work and live. In the army in India, British troops are more susceptible than Indians and in the former the incidence is highest during the first two years of service; after this there is another peak in the incidence curve at about 11 years' service. The high incidence during the first two years is undoubtedly due to lack of experience—of the heat, of how to mitigate its effects, and of mild infections, such as sandfly fever—and the second rise to increasing age, chronic disease, and possibly acquired bad habits, *e.g.* alcoholism. After middle-age, age itself is certainly a contributing factor.

The pyknotic individual is probably more susceptible than the asthenic, and obesity increases susceptibility.

Alcoholism and over-eating are detrimental. The teetotaller is undoubtedly at a great advantage in extreme conditions of heat, and alcohol should never be taken during the day in hot weather.

Other environmental factors.—In addition to climate the other important environmental factors are unsuitable clothes, ill-ventilation, and overcrowding (*e.g.* the historical 'black hole of Calcutta').

Ætiology

Physiology.—It will be necessary to refer back to the physiology of heat balance (*see* p. 7). To summarize, heat is formed by the normal body functions (100 calories per hour) and this heat production is markedly increased by work (marching with a pack of 65 lbs. produces nearly 500 calories an hour). The process of heat loss is *sensible*, that is, it is lost to the cooler immediate environment (by radiation and convection), and/or *latent*, that is, absorbed by evaporation (1 gramme of evaporated water absorbs 0.58 calorie). In a cool climate most of the heat loss is *sensible*, but, as the dry-bulb temperature of the environment nears 98.4°F., this means of heat loss is reduced until, when the temperature rises above this figure, *sensible* heat loss becomes heat *gain*. Above this temperature, all the heat loss will be *latent*, but as the humidity rises and the wet-bulb temperature nears 98.4°F. this means of heat loss is also reduced to *nil*, and eventually the body temperature must rise.

Air movement and clothing are also important factors and can be considered together. Provided the temperature of the air is below 98.4°F., air movement will assist *sensible* heat loss, and, as clothes impede the movement of air around the body, they interfere with this heat loss. At temperatures above 98.4°F. air movement increases *sensible* heat *gain*, but provided the air is dry it increases *latent* heat *loss*. Thus, air movement

usually increases total heat loss and clothes decrease it, but in **extreme** conditions of heat the reverse may be the case.

The important factors in heat balance are therefore *work, temperature, humidity, air movement, and clothing*, the last two acting in either direction, and these five become the important determining factors in heat imbalance, or hyperpyrexia. For expressing the combined effects of temperature, humidity, and air movement, a single unit, the effective temperature, has been introduced (*see p. 8*). An effective temperature of 97°F. is about the upper limit of tolerance of the body, even naked and at rest.

The following figures regarding the effect of different combinations of temperature, humidity, air movement, and work from various sources are worth quoting:—

In still air at rest it is just possible to survive—

a temperature of 100°F. when the humidity is 90 per cent.

"	"	120°F.	"	"	"	"	40	"	"
"	"	140°F.	"	"	"	"	15	"	"

In each case the effective temperature is about 97°F.

The body temperature will show a definite rise when the subject is—

at rest in moving air, at 93°F. wet-bulb temperature.*

" " " still " " 88°F.

doing moderate work in moving air, at 86°F. wet-bulb temperature,

or doing moderate work in still " " 78°F. " "

The adverse effect of hot winds in a desert area is shown by the observation that at 128°F. it is not possible to survive long in a wind of 20 miles per hour, whereas if the wind increases to 58 miles per hour long survival would not be possible even at 117°F.

Associated factors.—Of the *predisposing* factors, infection, usually—but not necessarily—with some organism that in ordinary circumstances would produce only a mild febrile reaction (*e.g.* influenza, dengue, sandfly fever), is undoubtedly the most important; others mentioned above include constitutional disease, obesity, old age, and alcoholism. A previous attack of heat stroke is usually considered to be an important predisposing factor; it seems very possible that this is the case, but the statistical evidence on this point might mean nothing more than that those who have had one attack are constitutionally ill-fitted to withstand high temperatures and are therefore likely to suffer again.

From another point of view, infection and the taking of alcohol might be considered to be the *determining* or *precipitating* factors; both are potent factors in upsetting the finely-balanced heat regulating mechanism when it is working under the strain of adverse environmental conditions.

The Pathological Processes associated with the Breakdown of Heat Regulation

A. Hyperpyrexia.—A slight temporary rise of temperature under extreme conditions is not pathological, but it becomes pathological when the compensatory mechanism fails to respond, through being defective or being strained beyond its physiological limits; then the temperature will rise, the heat regulating centre will be affected, there will be inhibition of sweating, and a vicious circle will be established. When the temperature reaches 108°F. neuroglobin is precipitated and irreversible changes in the brain and cord occur.

* The discrepancy between these figures and those shown in figure 2 are dependent on the fact that the latter were based on patients subjected to artificial hyperthermy and that a different criterion for a definite rise in temperature has obviously been taken.

B. Circulatory failure (heat shock).—In the attempt to get rid of heat, there is a very marked dilatation of the peripheral vessels and a very great loss of fluid in perspiration. One of the first reactions to a hot climate is an increase in blood volume (*vide supra*) which is apparently an attempt to meet the extra requirements of an increased vascular bed, but this extra fluid content of the blood is soon exhausted and dilution becomes concentration, so that eventually there is an increase in the vascular bed, a decrease in the blood volume, and an increase in the viscosity of the blood. This will lead to a fall of blood pressure and circulatory failure. The recovery from such a condition is complicated by paralysis of the vaso-constrictor mechanism, an expression of the general heat regulating failure. This circulatory failure is enhanced by the taking of alcohol and/or of a heavy meal, the latter causing splanchnic dilatation and a further increase in the vascular bed.

C. Electrolytic imbalance.—There is a continuous loss of chlorides and fluids in the perspiration; this fluid loss is usually replaced by pure water. It has been shown that the blood chlorides fall during the hot weather and are always at a low level in cases of heat hyperpyrexia. There is also a fall of plasma bicarbonate and an increase in lactic acid. Marsh (1937) gives the following mean figures :—

	Cold weather	Hot weather	Patients suffering from heat effects
Blood sodium chloride mg. per 100 c.cm. ..	494 \pm 38	466 \pm 29	448 \pm 52 (mean of 45 patients).
Plasma bicarbonate milli- mols per 100 c.cm. ..	2.78 \pm 0.26	2.54 \pm 0.18	As low as 0.61
Blood lactic acid mg. per 100 c.cm. ..	24 \pm 6	30 \pm 9	As high as 100

A better indication of the degree of hypochloræmia will be obtained from the urine. Even before the onset of symptoms this will be reduced from a heavy cloud of chlorides (on addition of silver nitrate—*vide infra*) to complete absence. There is also acetone and diacetic acid in the urine.

Severe muscular cramps are a clinical manifestation of this condition (*vide infra*, **Heat Cramp**).

D. Super-dehydration.—This is a most important factor in hyperthermia, but it is one which is overlooked with surprising frequency. It is of course particularly in evidence when conditions prevent fluid replacement. The blood, organs and other tissues all suffer; the effect on the blood is reflected in the circulatory failure noted above, and the parenchymatous changes that are reported in the organs, *e.g.* the kidney, are probably due to this dehydration, at least in part. After dehydration has reached a certain point sweating ceases and little further evaporation is possible.

All these conditions are frequently produced in a single case of heat ill-effects but at any one time there is usually emphasis on one particular process and the symptoms will vary accordingly.

Morbid Anatomy

There is usually a marked post-mortem rise in temperature, but this will occur in other conditions and cannot be considered pathognomonic of death from heat hyperpyrexia. There is very early post-mortem rigidity, and this may also seem to appear ante mortem in subjects who have been seriously dehydrated. The skin and mucous membranes are cyanotic, and

there may be a petechial rash. There is hyperæmia of all the organs, and particularly of the meninges which in certain instances also show œdema. The heart is stopped firmly contracted in systole, and the blood in the vessels is dark and viscid suggesting tar in appearance and consistency.

Microscopically, there are punctate hæmorrhages in the muscles, in the organs, and in the serous membranes; degenerative changes are seen in the nerve cells, and parenchymatous degenerations in the various organs have been described, but these are very probably post-mortem changes, for at such temperatures these changes occur almost immediately the patient dies.

Symptomatology

The onset.—When the patient is already under observation, the onset of the symptoms may be noted from the beginning, and if circumstances permit, the attack can usually be aborted. On the other hand, it may be more insidious so that the patient does not notice the symptoms himself, or probably more often refuses to 'give in', or on account of the circumstances is unable to do so, until he suddenly collapses or passes into a state of maniacal excitement. The stages of the attack are as follows:—

Early and prodromal symptoms.—The patient who is working up to an attack of heat hyperpyrexia will have a flushed and cyanosed appearance, his conjunctivæ will be red and his pupils contracted, and his skin will be intensely hot and dry; he may be drowsy, or uncomfortable and restless; and he will complain of a severe headache, of a constriction of the chest, often of frequency of micturition, and sometimes of a watery diarrhœa and vomiting. At this stage the pulse rate will be slightly increased and the temperature raised (but this may be due to the infection for which he is already under medical observation, and it is mainly in such cases that the early symptoms will be observed).

Second stage.—Nearly all the signs and symptoms of the early stage are increased, drowsiness or slight restlessness turn to marked hysterical excitement amounting to mania in many cases; the urine becomes scanty and if tested will show a distinct cloud of albumin; the pulse is now full and rapid and the respirations increased, and the temperature is beginning to mount rapidly. The knee jerks may be lost at this stage.

Final stage.—This is very often the stage at which the patient is first seen. He is unconscious and often delirious, he has a burning skin, a cyanosed face, suffused conjunctivæ, bounding pulse, stertorous breathing, and the temperature may be to 108°F. or higher. All reflexes are lost. The unconsciousness deepens to coma, the breathing becomes Cheyne-Stokes in character, and he dies with a temperature sometimes as high as 115°F. in the rectum (117°F. has been recorded).

Heat shock.—The first sign of the effects of heat may be syncope, later to be followed by hyperpyrexia; on the other hand, syncope may be a phase of the general condition, or it may result from too vigorous treatment in the hyperpyrexial stage. There is collapse, vomiting, and dyspnœa; the pulse is feeble, the systolic blood pressure falls to 70 mm. Hg. or so, and the rectal temperature may be low, but quite often the temperature in the rectum still remains high.

Diagnosis

The diagnosis is complicated by the fact that in the vast majority of cases the patient is suffering from some other condition as well, and it is difficult to apportion the responsibility. However, if on a hot day a patient has hyperpyrexia, or if he is brought in unconscious with no obvious signs

of trauma, vigorous treatment must be applied for the hyperpyrexia or the collapse, immediately, whilst attempts are being made to exclude other conditions; the most important ones to exclude—as in these cases other vigorous action is indicated—are malaria, and diabetic coma or hypoglycæmia. Other conditions that are likely to give rise to symptoms suggestive of heat shock are cerebro-spinal meningitis, dengue, sandfly fever, typhoid and other febrile diseases, apoplexy, epilepsy, and uræmia.

Prevention

Some of the ways of mitigating the effects of heat have been discussed above (*see p. 16 et seq.*).

The methods adopted will naturally depend almost entirely on the circumstances. For meeting any particular set of circumstances the factors in the production of heat stroke should be kept in mind. For example, though it may be impossible to lower the temperature it may yet be possible to reduce the humidity and increase air movement (by ventilation), in most circumstances it will be possible to reduce the hours or the amount of work, and almost always to modify the clothing suitably (an exception to this last is the case of A.R.P. workers who may have to wear asbestos or rubber clothes and masks to protect themselves from fire and gas). Work in particular should be graded to meet the environmental circumstances. The soldier who is under training should have his hours of work in the heat of the day reduced in the hot weather, and in India there is an arrangement in operation by which the meteorological department warns the military authorities when the temperature is likely to be particularly hot, so that they do not embark on any strenuous military exercises during this time, or, if they think that such exercises in hot conditions constitute an important part of the soldier's training, at least they can grade the strain imposed on the raw recruit.

This brings one to the matter of **acclimatization** (*see also p. 17*). The general whose soldiers can fight in all circumstances has obviously a great advantage in real warfare, and in industry there is much work that has to be done under adverse conditions. Much can be done by increasing the hours of work in trying circumstances very gradually, and the Germans are reported to have arranged hot chambers, in which the soldier has to work for gradually lengthening periods, for training their soldiers to withstand high temperatures, *before* they go to hot climates, *e.g.* North Africa. The armies of the British Empire are more fortunately placed in being able to train many of their soldiers in hot climates.

In mines, in which work has to be done at a great depth where it is very hot, miners are acclimatized gradually by being put to work in the cooler seams at first and then being transferred to the deeper ones, and also by having their output of work in the hotter seams graded. It has been found that after long spells of leave re-acclimatization is necessary.

During short periods of exposure to heat, food may be reduced to a minimum and should be predominantly carbohydrate, but in longer periods of exposure a balanced diet up to the full caloric requirements—which are slightly lower than in temperate climates—must be taken. Heavy meals during the heat of the day should always be avoided.

The **fluid** intake must be studied; at least eight pints of fluid should be taken, and for those doing hard manual work in very hot climate, figures of 24 (Hunt, 1912) and 33 pints (Scholl, 1937) have been advocated.

The importance of avoiding dehydration cannot be over-emphasized; it should be remembered that the sick—and more especially the wounded

suffering from shock—may not ask for water, and they must therefore not only be allowed as much water as possible but must be pressed to take it.

The salt requirements will be from 10 to 20 grammes a day and more in special circumstances; this may be taken in the food or with the fluid. With such large draughts of water it is absolutely essential to increase the salt intake and the addition of half an ounce of sodium chloride to each gallon of water has been recommended, but this makes an unpleasant drink and a better plan is to take three 10-grain tablets of salt with each pint of water drunk. Alcohol should be avoided during very hot weather and should certainly not be taken during the day.

When the question of salt intake is in doubt, the urine should be tested for chlorides; the urinary chlorides should not be allowed to fall below 0.5 per cent.

Test for chlorides in the urine.—The following simple test is a very useful one for the ward or clinical laboratory. The reagents required are potassium chromate 20 per cent, and silver nitrate 2.9 per cent. The test is carried out as follows:—

Ten drops of urine are taken in a test-tube and a drop or so of potassium chromate added. The mixture is well shaken. The silver nitrate solution is then added drop by drop, the test-tube being well shaken after the addition of each drop. At a certain point the solution will turn brown, and remain brown after shaking. This is considered as the end-point of the test.

The same pipette, held at the same angle, preferably vertically, must be used for measuring the urine and the silver nitrate. After it has been used for measuring the urine, the pipette must be washed out first with distilled water and then with a small amount of silver nitrate. The potassium chromate is only an indicator and need not be measured accurately.

The calculation is made from the number of drops of silver nitrate added to 10 drops of urine *before* the colour changes to brown, one drop representing 1 gramme of chlorides, calculated as NaCl, per litre; that is, if the 7th drop turns the solution brown, the amount is 6 grammes per litre, or 0.6 per cent.

In a normal person, 8 to 10 drops will be added before the solution turns brown. In a dehydrated and hypochloræmic patient, the brown colour will sometimes appear after the first drop, indicating that there are practically no chlorides present in the urine.

In every large hospital in a country where heat stroke is common, there should be an air-conditioned ward in which the temperature is kept within the comfort zone. This is particularly important in connection with industrial concerns where the work may entail subjection to temperatures even higher than that of the already high atmospheric temperature. Heat stroke subjects can then be admitted straight into such a ward and the lowering of their temperatures is considerably facilitated. Further, hospital patients showing the first signs of the failure of the heat-regulation mechanism can be transferred to the air-conditioned ward.

Much can be done in a hospital by keeping an intelligent watch on all febrile patients, and very frequently, even in the absence of an air-conditioned ward, it will be possible to abort the attack. Careful watch should also be kept on the urine to be sure that it contains the normal quantity of chlorides, and, if it does not, the salt intake should be increased.

In industrial concerns, the medical officer should see that the environmental conditions are improved as much as is practicable (*e.g.* by artificial ventilation), that the work of the new recruit is graded, that the health of the labour force is maintained at the highest level by other sanitary measures (*e.g.* anti-malarial), that the worker's nutritional requirements are adequately met, and that he is supplied with plenty of safe fluid throughout the day (*vide supra*).

Treatment

The patient must be removed by the fastest means possible to a hospital or at least to some cooler place. If he is already in hospital he should be moved to an air-conditioned room—if there is one—or to the coolest place available.

All the *physical* means possible must be brought into action to bring down the temperature, but drugs must be avoided at this stage. Hydrotherapy offers the best opportunities, cold baths, cold wet sheets, and ice packs, when ice is available, must be used freely; a hand or electric fan should be used to aid the cooling. Cool enemata and cool intravenous salines may also be employed; a note of warning regarding the former is necessary, because the rectum is the best temperature indicator from which one ascertains the point at which the cooling treatment is to be discontinued.

Massage is of great value in both the hyperpyrexial and the collapse phases. It is important to maintain the circulation in the former phase, so that the cooled peripheral blood is conveyed rapidly to the internal organs, and, in the latter, it will naturally form part of the treatment for shock.

The life of the unconscious person with heat stroke will depend on the early reduction of temperature, so no possible means of lowering the temperature should be neglected; once, however, the temperature has been reduced to 102°F. in the rectum, vigorous measures should be discontinued, and the patient left in bed covered by a sheet or a light blanket, but he must be carefully watched to see that, (a) his temperature does not rise again, and (b) that he does not collapse and pass into a state of heat shock: It is by no means an uncommon experience for a patient—especially one whose heat-regulating mechanism has been upset by some infection—to see-saw between hyperpyrexia and heat shock throughout the whole day, and when—as happened many times in Iraq, in the writer's experience during the 1914–18 war—a number of patients in the hospital are doing this, the amount of work that falls on the staff may well be imagined.

For intravenous use, alkaline saline (sodium chloride—90 grains, calcium chloride—4 grains, and sodium bicarbonate—160 grains, to a pint of water) should be given at a temperature of 60°F.; this has the effect of lowering temperature, helping the circulation, counteracting both the chloride loss and the acid increase, and combating dehydration, so that it helps to counteract all four pathological processes mentioned above. Warm (room temperature) intravenous alkaline saline will also be valuable in the collapse phase.

Drugs should be avoided as far as possible. No antipyretics must be given, and other drugs strongly contra-indicated are strychnine and atropine, the former because it will increase the neuro-muscular tonicity and exaggerate cramps, and the latter because it inhibits perspiration. Of the stimulants, caffeine, camphor and ether in oil, and coramine can be used, in that order, and with regard to sedatives, in cases of acute delirium, chloral and bromide can be given per rectum; phenobarbitone is the safest effective drug for severe headache, and it may also be used for sleeplessness, if bromide and chloral (10 grains of each) fail.

In patients in whom the blood pressure is high and there are signs of congestive heart failure, **venesection** should be considered, and, in unconscious cases with signs of cerebral irritation, lumbar or cisternal puncture

may be advisable. In the former case, the blood should if possible be taken into citrate saline, so that if the state of the patient changes over to the collapse phase later, it could be returned to his circulation.

In the **shock** phase, whether it is the initial state or has followed hyperpyrexia, treatment is very much the same as for any case of shock, but the danger of pushing the patient over to the hyperpyrexial phase must always be kept in mind, and all measures that are aimed at increasing body temperature must be applied with great caution. The treatment will include nursing in the horizontal position, massage, possibly hot-water bottles, intravenous saline or 5 per cent glucose, and of drugs, cortin or the synthetic desoxycorticosterone acetate, pituitrin and adrenalin.

Diet.—If the patient is conscious, he should be made to take fluids freely by the mouth, with glucose and sodium bicarbonate, and, if there is any chloride deficiency in the urine, sodium chloride up to two ounces in the twenty-four hours, must be given. The question of diet need not be considered for twenty-four hours and then a fluid diet should be given for a day or two before the patient is allowed to return gradually to his full diet.

Convalescence.—This will depend on the gravity of the attack, but in any case the patient should not be allowed to return immediately to the environment in which the attack occurred, or to full work. He should, if possible, have a holiday in a cool and quiet place, live on a low diet, take no alcohol, and pay special attention to his personal hygiene, including keeping his bowels well regulated. If it is thought advisable for him to return to his previous environment and work, he should at first return but do little or no work, then gradually increase his hours of work, and, if he is employed on manual labour, the actual amount of work done should be graded.

Prognosis and sequelæ.—Prognosis will depend almost entirely on the rapidity and efficiency with which treatment is carried out. Rogers reported 8.3 per cent of deaths in patients whose temperature did not rise above 107°F., but when the temperature rises above 107°F. or the patient remains unconscious for more than three hours the prognosis is bad, and, even if he recovers, he may suffer from the permanent effects of damage to nerve tissue. The factors that militate against recovery are previous hypertension, and the complication of some serious febrile infection, such as typhoid.

Sequelæ include long periods of low fever, headaches, myocardial weakness, enfeebled intellect, and sometimes dementia; according to Rogers the last occurs in about 10 per cent of severe cases of heat stroke. After an attack of heat stroke the subject is said to be much more liable subsequently to the effects of heat.

B. Heat Exhaustion

The **epidemiology** of this condition is naturally closely allied to that of heat stroke, but there are differences. For example, women are more liable to suffer from heat exhaustion than from heat stroke, and indolence is almost as likely to cause it as work. However, the male worker is also liable to heat exhaustion which is very often a prodromal stage of heat stroke, or it may be looked upon as a mild attack of heat stroke.

The **ætiology** is virtually the same, but there is more often a psychological element in heat exhaustion.

Some sojourners appear to suffer from a form of thermal instability; the defect in their heat regulation mechanism is probably congenital in

the majority, but in a few it appears to be acquired after some serious febrile affection such as typhoid or heat stroke.

The **symptoms** include weakness and lassitude, headache, dizziness, diarrhoea and vomiting, mild cramps, and sleeplessness. A rapid pulse, low blood pressure, and low fever will probably be the only clinical findings. Chlorides will usually be low and may be absent from the urine. In the case of the worker, the first evidence may be that he faints at his work.

Some degree of anæmia will often be found, and it must be looked upon as a contributory cause and due to some other ætiological factor, possibly of dietetic origin.

In the thermal instability form, the patient's temperature will rise to 102°F., or higher, every year, when the effective temperature goes beyond a point, say 85°, at which most people are uncomfortable but able to compensate it. These patients are often diagnosed as enteric, though they don't usually feel very ill, and the writer has recently had a patient who was treated as enteric 5 times in 7 years. Many children's temperatures will always rise two degrees or so in the middle of the day in the hot weather, without there being any discoverable cause.

Amongst patients with this condition, there will be a good proportion of neurasthenics and malingerers, but care must be taken that the genuine cases are not classed amongst these.

Treatment of the milder cases consists in removal of the patient from the surroundings that caused the condition, very careful investigation for some underlying disease, regulation of the diet and fluid intake—not forgetting the salt requirements, regulation of the bowels, and finally the administration of some tonic mixture.

In the more severe cases the treatment will approximate to that given for heat stroke.

C. Heat Cramp (or Stoker's Cramp)

The excuse for allowing this symptom of the general syndrome of hyperthermia a separate heading is that it has a clear-cut ætiology and that it is very often the only symptom. It is due to excessive perspiration and the replacement of the lost fluid by drinking pure water, so that the chlorides lost in the perspiration are not replaced. Heat rather than humidity is the important factor and cramps seldom occur if the temperature is below 100°F. There are no special predisposing factors unconnected with salt intake, except conditions in which vomiting occurs; here the further loss of chlorides in the gastric juice increases the deficiency.

The cramps usually occur in the muscles that are most used. They may start either during work or some hours after work has ceased. As well as those of the fingers—especially the flexors—fore-arms, arms, and legs, the muscles of the pelvic girdle and abdomen are sometimes affected. The involuntary muscles are never affected.

The muscle contracts to an iron-like hardness and during the time of the contraction the pain is agonizing, so that it is quite impossible for the patient to do anything or even to maintain a conversation. When the contraction passes the pain is immediately entirely relieved, but the muscles remain very tender for some time afterwards, up to a few days. The spasm may be started by active movement, by a knock or even by a cold draught playing on the skin over the muscle.

There is not necessarily much diminution in the urinary output, but there may be complete absence of chlorides from the urine. The blood changes include an increase of plasma protein, and of plasma potassium, phosphorus and calcium, and a marked diminution in plasma sodium. There is also an increase in cell volume percentage.

Prophylaxis has been discussed above. The most important feature is the provision of saline drinks. Ten grains to the pint makes a reasonably palatable drink, but this may not be sufficient. The taking of three 10-grain tablets with each pint of water is an additional precaution that may well be observed.

Treatment consists in giving copious saline draughts, and intravenous and rectal saline, if necessary. In severe cases, it may be necessary to relieve the cramps by giving morphia, or whiffs of chloroform.

The similarity of this condition to hyperventilation tetany has been pointed out recently, but it seems unnecessary to suggest that the physiological hyperventilation which occurs in a hot climate is likely to be the cause of the cramps when there is a much better explanation.

Morbus Britannicus is an allied condition that was at one time common amongst British sailors. It was due to loss of chlorides in perspiration and vomitus; it is usually, but not necessarily, associated with a hot climate. It received its name from the fact that Scandinavian sailors who lived on salt meat seldom suffered from it, whereas it was common amongst British sailors who lived on fresh meat.

The abdominal muscles are usually affected—because of the important part played by vomiting—and the condition often simulates an acute abdomen.

PATHOLOGICAL CONDITIONS PRODUCED BY THE ULTRA-VIOLET AND LIGHT RAYS OF THE SUN

One of the main effects of the ultra-violet rays is physiological, the conversion of the cholesterol of the subcutaneous fat into vitamin D. The pathological condition hypervitaminosis D is recognized, but it is doubtful if it could ever be produced by the action of the sun's rays alone.

Solar dermatitis—the French *coup de soleil*—is a condition that is actually produced by the ultra-violet rays though the other sun's rays probably play some part in sensitizing the skin to the effects of these rays. After over-exposure to the sun's rays, the first effects will appear in about two hours and the maximum effects in about six hours. At first there is erythema, then a hyperæmia of varying intensity up to a serious congestion with œdema which may be followed by blistering; there is in any case a superficial necrosis of the epidermis, which eventually separates, as in a burn of the first degree, leaving the deeper layers of the skin exposed to the risk of secondary infection. The immediate inflammatory reaction may be a serious one causing severe pain locally, high fever, and toxæmia; even more serious results may follow secondary infection. Thus, though the condition is usually treated lightly and often jocularly, a severe sun-burn may have a fatal result.

The parts most likely to be affected are the uncovered areas of skin on which the sun's rays fall vertically, the upper part of the forehead, the nose, and the malar eminence, the back of the neck and shoulders, the backs of the hands and the dorsa of the feet, and the knees and the fronts of the thighs if the exposure was in the sitting posture. A single layer of clothes, even a thin handkerchief, will usually give complete protection.

Sun-burn is usually the effect of direct sunlight, but serious sun-burns will also result from the reflection from snow or desert sand, and on a dull day the same effect may be produced by reflection from the clouds, so that care should be taken not to leave a sensitive patient on the verandah on such a day. In the case of snow-burn the lesions will be mainly on the neck, the chin and lower part of the face.

In specially sensitive individuals an urticaria sometimes develops on areas exposed to the sun; the condition has been called 'urticaria solaris'. Rays between 3,800 and 5,000 Å are thought to be responsible for this somewhat rare effect (Arnold, 1941).

Frequent exposure to the sun's rays will eventually lead to the deposition of pigment, which gives some protection to the skin during subsequent exposures. Whilst the rays between 2,800 and 3,100 Å are the most potent in the production of erythema, the longer, light rays are more active in the production of pigment. Repeated irritation from over-exposure to the sun's rays will produce keratosis and a pre-cancerous condition which may eventually develop into **rodent ulcer** or **epithelioma**, conditions that are common amongst men of European descent living open-air lives, in Australia for example.

The natural pigment of the dark-skinned races protects these subjects to a large extent from these effects, and amongst fair-skinned races the brunette is less susceptible than the blonde (*vide supra*). Certain substances sensitize the skin to the effects of the ultra-violet rays; for example, that inborn error of metabolism, hæmatoporphyrinuria, and Kaposi's disease make the unfortunate victims of these conditions extremely sensitive to the sun's rays all their lives, and the dermatitis of pellagra is probably due to coproporphyrinæmia. Certain protein decomposition products and bacterial toxins also hypersensitize the skin, so that special care should be exercised in exposing sick persons to the sun's rays and in the administration of artificial light therapy to them.

Amongst drugs, the heavy metals that are used for injection, *e.g.* gold, and substances that have fluorescent properties, *e.g.* dyes, such as trypanflavin, used in the treatment of brucella infections, cause sensitization.

Prevention does not present any great difficulties; a single layer of clothing, even a silk handkerchief, for example, or a thin layer of any oil will protect the skin from sun-burn. Ordinary yellow vaseline, or 2 per cent tannic acid and 10 per cent castor oil in spirit as a prophylactic paint, are quite as good as any of the more expensive preparations that are advertised. Usually the main difficulty is to keep the application from being washed away by the sweat, or absent-mindedly wiped away when the face is mopped.

The **treatment** of sun-burn is purely palliative; cold cream or calamine lotion are probably the best substances to apply. The more serious lesions must be treated as burns, with 2 per cent tannic acid and 10 per cent silver nitrate spray, with the triple dyes, or with whatever is the treatment indicated by the distribution of the lesions.

Light-stroke, or severe form of **sun-headache**, is a common and sometimes serious syndrome amongst newcomers to the special environmental conditions that produce it. In this case, it is in almost every instance the reflected light rays from snow, desert sand, bare baked earth, and water surfaces, rather than the direct ones that are mainly responsible.

The symptoms produced are intense headache, vomiting, prostration, and fever. Much of the so-called 'sunstroke' of a few decades ago was undoubtedly this condition, and today the layman still attributes his symptoms to failure to keep his head or the back of his neck covered. The local effect on the retina is a reduction in visual acuity which may be considerable and in extreme cases may amount to complete blindness; this is usually temporary and from all the milder degrees of the condition complete recovery may be confidently expected.

The direct and indirect glare from the tropical sun undoubtedly play a part in the production of **night-blindness**. Though this condition is more often due to psychological causes, strong light breaks down the visual purple in the retina which is again formed with the aid of vitamin A. When the diet is deficient in vitamin A, night-blindness results. Other eye symptoms of vitamin-A deficiency are Bitot's spots (white or yellowish foam-like patches on the cornea), xerophthalmia (dryness of the cornea), and keratomalacia (softening of the cornea). Anæmia-producing conditions, such as hookworm disease and malaria, also increase this tendency to night-blindness.

Prevention consists in the wearing of suitable tinted glasses. In the green tropics Calobar-D lenses are suitable for general use and it is a mistake to have glasses unnecessarily dark, as this leads to eye-strain when objects have to be viewed accurately, but in desert areas much darker glasses may be necessary.

Treatment consists in rest in a darkened room. Phenobarbitone should be given to relieve the severe headache, and for the prevention and treatment of night-blindness, a liberal mixed diet with the addition of vitamin-A concentrate, if the diet is thought to be deficient in this vitamin; the fish-liver oils are the best animal source of the vitamin proper, and red-palm oil the best vegetable source of carotene (or pre-vitamin A) from which the vitamin is synthesized in the body. Any associated anæmia should be treated appropriately.

OTHER CONDITIONS THAT ARE ATTRIBUTED TO TROPICAL CLIMATE

Tropical Anæmia

It is now well established that no such condition exists. It is however only during the last few years that the fallacy that residence in the tropics invariably leads to a 'thinning of the blood' has been exploded and that the home-returning sojourner has ceased to drink nightly a glass of port wine—the hæmatinic value of which is incidentally more than questionable—to counteract this thinning, as his ship enters temperate waters. The hæmoglobin content of the blood of the healthy sojourner is higher than of people of his class in temperate climates; if it is not, the reason for this should be sought and will often be found in some sub-clinical infection or dietetic deficiency. The hæmoglobin level of the indigenous inhabitant is also certainly not lower than that of the European standards (*vide infra*).

Tropical Neurasthenia

The term 'tropical neurasthenia' is one that has come into general use, without a very exact definition being attached to it and certainly without any clear understanding regarding its ætiology. Many practitioners have encountered mild psychasthenic conditions amongst their patients and have labelled them tropical neurasthenia, but, as far as we know, no series of cases has been studied and no scientific data regarding the most commonly associated physical conditions or even the environment in which tropical neurasthenia most frequently occurs has been collected.

It is doubtful if it is ever due to the direct effects of heat alone, though it is probably most commonly encountered in hot damp monotonous climates in which there is little seasonal variation. Again, climate is certainly not the most important factor, nor are the conditions with which it is associated found only in the tropics, though most of them are probably more frequently encountered in a tropical than in a temperate climate, a circumstance which provides the only justification for the term tropical neurasthenia.

The ætiological factors can be grouped under the following heads and if the author were compelled to assign the degrees of importance to these factors he would give the percentages as indicated below :—

(a) Physical—disease or fatigue	50 per cent
(b) Heredity	20 „ „
(c) Social and environmental conditions	15 „ „
(d) Mental strain—overwork and over-responsibility	5 „ „
(e) Alcoholism and drug addiction	5 „ „
(f) Climate <i>per se</i>	5 „ „

(a) *Physical*.—Under this heading, bowel conditions undoubtedly head the list. The commonest history is one of repeated attacks of dysentery, followed by a condition of chronic diarrhœa with mild abdominal pain and discomfort. The patient may have a chronic amœbic infection but quite often he has not.

His attention becomes centred on his bowels and his diet; in his over-anxiety to rectify the bowel disorder, he often remains on a low fluid diet for long periods and this leads to specific malnutrition of the bowel wall, stasis, fermentation and dilatation, a condition of dysfunction of the small intestine, which may or may not be associated with ulceration of the large gut, and anæmia.

Unsuitable, indifferent and monotonous food served in depressing surroundings that is liable to be the lot of the isolated bachelor will often result in loss of interest in food and the necessity to stimulate this by alcohol; this sequence again will lead to a state of undernourishment.

Debilitating febrile conditions, such as malaria, also predispose to neurasthenia, especially when frequent relapses occur, and both dengue and sandfly fever are particularly liable to lead to a state of depression and melancholia, which is sometimes so extreme that it may end in suicide. Finally, overdosage with certain drugs, especially quinine and emetine, in the former case usually self-prescribed, may be important factors in producing the condition: emetine is probably the most valuable drug after the cinchona alkaloids, in tropical practice, but it is certainly the most abused.

A phase that follows a run of ill-health is the patient's fear of being ill again and this may be accompanied by worry that he is not doing his work and earning his pay, or, more egotistically, that he will lose his appointment. This phase is usually much more highly developed in the married man with children.

Fatigue may result from physical overwork, or the mistaken idea that exercise is the cure for all ills.

(b) The influence of *heredity* will not be avoided by sending the patient abroad, as the heads of families—ill-advisedly encouraged by their family doctors—sometimes appear to think, or perhaps only hope. This expedient often presents an easy way of getting rid of a grown-up 'problem child'. Or, the weaker type of man hopes to escape from the speed, bustle, and competition of life in the west by coming out to the

tropics, where, however, he finds that other qualities, which also quite frequently he lacks, are necessary, and again he has to face the fact that he is a failure.*

Medical men who pass recruits for the tropics should pay particular attention to this aspect of their examination.

(c) A young man comes out directly from school or college—this applies to both sojourners and educated natives of the country—and finds himself in some isolated spot many miles from the nearest potential companions, where he lives in uncomfortable and depressing surroundings, with only his servants or the subordinate staff to talk to. Further, if he is unmarried he will either suffer from sexual starvation, or if he cohabits with a local woman, necessarily of the lower classes, though he may get a little crude sexual relief, he will get no sexual companionship and may suffer from a sense of shame which will make him introspective and unsociable. On the whole, therefore, even if he escapes venereal disease, his case will be a worse one than if he remains celibate.

On the other hand, if he is happily married and has children, he has their illnesses and that of his wife to worry about as well as his own. Finally, unhappy marriages are a very common cause of neurasthenia in either or in both partners.

(d) *Mental strain* is a common cause of neurasthenia in any climate. However, in the tropics, young and/or inexperienced sojourners are more often suddenly thrust into positions of considerable responsibility, or of special danger, for which they are not really fitted, and the experience is sometimes too much for them.

(e) *Alcoholism* is probably more often a manifestation, or rather a stage in a vicious circle, of neurasthenia, than a cause of it. The unstable individual seeks, in alcohol, solace in his solitude, escape from his physical, matrimonial, or other troubles, or stimulation in his exhaustion; this subterfuge may work for a time, but eventually it fails, and leaves the victim in a neurasthenic condition.

Drug addiction is not common in sojourners, but cannot be excluded as a cause of neurasthenia.

(f) Probably the only direct effect of *climate per se* in this capacity, except in very extreme conditions, is by interfering with rest at night.

In women.—The causes of neurasthenia are naturally different in men and women. In the latter, health plays an even more important part; anxieties regarding the health of children or separations from children are also more prominent factors; and sexual neuroses are probably more common in women.

Actual fear of servants, native neighbours, snakes, insects, etc., is probably a factor more or less confined to women. Idleness and boredom replace overwork as factors. Alcoholism is probably less common amongst women but cannot be excluded, and is to some extent replaced by 'chair smoking'.

Symptoms.—These do not differ materially from those exhibited in a temperate climate, and will vary with the ætiology. Headaches, sleeplessness, inability to concentrate and loss of memory, indecision—even in such an unimportant matter as to whether to use a spoon or a fork—loss of

* On this subject, Professor Culpin (1939) says 'there is a selective tendency a work by which home-misfits vainly seek a new environment for their mal-adjusted personalities'.

emotional stability, hypochondriasis, and acute depression—even to the extent of committing or attempting suicide—are some of the common symptoms. Frequently there will be tachycardia, a subnormal or an unstable temperature (*i.e.* one permanently raised about a degree above normal in the hot seasons), a blood pressure on the low side, and sweating of the palms. Reflexes may be exaggerated.

Treatment.—There is no specific line of treatment, and perhaps more than in any other condition is the doctor-patient relationship of the utmost importance. It is essential that the patient should have complete confidence in and respect for the doctor, and for this reason if the doctor is already on too familiar terms with his patient, he should consider the advisability of sending him, or her to some other doctor, with very full confidential notes and possibly even recommendations as to the line of treatment.

A sympathetic appreciation of all the patient's symptoms is essential but care should be taken not to be too mysterious about these, or he may suspect that he is suffering from some serious condition which is being hidden from him.

Hypochondriasis often merges into neurasthenia and it is sometimes a good plan to send a patient to some medical institution for a 'thorough investigation'. This will have a double effect; some unsuspected underlying cause, *e.g.* a protozoal or helminthic infection, gastric dysfunction or gall-bladder infection, nasal sinuses, tonsils or teeth infection, an error of refraction, or even some easily corrected blood dyscrasia, may be found, or, if nothing is discovered as a result of various investigations, the patient's confidence in his own health may be restored. Naturally, whenever possible, these investigations should be carried out by the doctor himself; capital should be made out of any discovery however trivial and very thorough treatment given in the case of any important finding.

The insomnia should be tackled first by investigating the environmental conditions associated with it, to see if any improvement can be effected. Light, noise, and other disturbing factors should be excluded to the maximum extent possible. Air-conditioning should be considered, even if it imposes an economic strain on the patient (*vide supra*). The patient's habits should then be enquired into and adjusted; his evening meal should be taken before 7-30 p.m. if he is going to bed at 10-30 o'clock. It is a mistake to think that going to bed later will help him to sleep, as exhaustion prevents rather than aids sleep. A hot bath immediately before going to bed will help some people. Before putting out his light, he should take a warm drink, alcoholic (hot 'toddy', made with whiskey, lemon and sugar) or non-alcoholic (milk, or some milk preparation) according to the patient's habits.

Drugs will usually be necessary and should be given in such a form that the dose cannot be gauged accurately by the patient, that is, either in mixture or in cachet form. A large and effective dose should be given at first and, when the habit of sleeping is acquired, the dose can be reduced.

R Chloral hydratis ..	gr. xv	Spiritus ammonii aromatici ..	3ss
Potassii bromidi ..	} 30 gr. x	Syrupi aurantii ..	3i
Ammonii bromidi ..		Aquam chloroformi ..	ad 3i
Sodii bromidi ..			

To be taken at bedtime, with a dose put ready to be taken 2 to 3 hours later if necessary.

Phenobarbitone gr. ii and paraldehyde 3ii are alternatives. Later, the chloral hydrate in the bromide mixture can be replaced by aspirin gr. x, and this sleeping draught continued for some time.

If no cause for the headache can be found, APC powder (aspirin gr. x, phenacetin gr. iii and caffeine gr. ii), Veganin, or Saridon should be tried first, and if these fail stronger drugs such as phenobarbitone may have to be used.

Whilst sedatives are usually indicated at first, later, when the insomnia is under control and there is some general improvement in the mental condition, tonic mixtures should be prescribed. Some of the proprietary mixtures, *e.g.* metatone, are useful in this connection.

A change of environment to a cooler climate is the obvious treatment for a neurasthenic, but this measure should not be resorted to until some attempt has been made to cure or counteract the underlying cause, or causes. If the patient is a sojourner and his home leave is due, he should certainly be sent home, but, if not, a month or two in a suitable hill station, or a short sea trip, preferably away from wife, or husband and/or children, as the case is, may be sufficient, but care should be taken to choose a place where the patient will find suitable amusement and exercise; it is no help to a neurasthenic with dyspsomaniacal tendencies to send him to a hill station to spend his time in the club bar!

Tropical Liver

This popular term describes a condition, probably commoner in the tropics than in temperate climates, that is not easy to define in medical terms.

Heavy functional demands on the liver lead to a condition of hyperæmia, which is within physiological limits at first but later becomes a pathological congestion; as well as being a troublesome minor malady, the condition is of importance because it predisposes to hepatitis and liver abscess.

Ætiology.—There are many factors other than climate that lead to this condition; in the sojourner, the most important are an unsuitable, high-protein and high-fat diet, heavy wines and alcoholic excesses, and parasitic infections, mainly malaria and amœbiasis. Lack of exercise is also a factor, especially in women, but this should not be allowed to dominate the mind of the physician, or the patient as it is liable to do. Up to a certain point, early morning exercise will mitigate the ill-effects produced by other factors, particularly those caused by gastronomic and alcoholic indiscretions, but at a certain stage this expedient will fail, and will, in fact, exaggerate the symptoms.

In the indigenous tropical resident, on the contrary, an excessive carbohydrate diet with a low-protein intake and vitamin deficiencies lead to a similar condition, and here again parasitic infections are very important.

The main **symptoms** are headache, dirty tongue, loss of appetite, general tiredness, sudden attacks of sleepiness, and a feeling of weight below the diaphragm. There is usually some tenderness in the liver region and possibly slight enlargement, a general unhealthy coloration of the skin, and sometimes an icteric tint of the sclerotics.

Prophylaxis consists in adjustment of diet and habits, and an occasional dose of sodium sulphate 3ii with sodium bicarbonate 3ii in a glass of hot water first thing in the morning. The regular taking of salts in the morning is a habit that is very easily acquired and is not a good one, as it is very liable to lead to constipation.

Treatment should first be directed at the elimination of any parasitic infection. As a general measure, after the diet has been adjusted, divided doses of calomel should be given at night, gr. $\frac{1}{4}$ every half hour up to six doses, followed by salts in the morning, and then for a week a nightly pill:—

R. Pilulae hydrargyri	gr. iv
Extracti aloes	gr. ii
Extracti hyoscyami siccati	gr. i

Empirically, a course of three daily injections of emetine gr. i is remarkably effective in this condition, but the patient should be confined to bed or to his house during these three days, and he must be particularly warned against taking exercise for a day or so afterwards. Emetine is a very valuable alkaloid, but it is a very dangerous drug when it is abused.

REFERENCES

- | | | | |
|----------------------|----|----|---|
| ARNOLD, H. L. (1941) | .. | .. | Urticaria solaris. <i>Arch. Derm. Syph.</i> , 43 , 607. |
| CULPIN, M. (1939) | .. | .. | Medical Industrial Psychology. <i>Report on the work of the London School of Hygiene and Tropical Medicine, for 1938-39</i> , p. 34. |
| HUNT, E. H. (1912) | .. | .. | The Regulation of Body Temperature in Extremes of Dry Heat. <i>J. Hyg.</i> , 12 , 479. |
| MARSH, F. (1937) | .. | .. | Heat-stroke and Heat-exhaustion. <i>British Encyclopædia of Medical Practice</i> , 6 , 396. Butterworth and Co., Ltd., London. |
| SCHOLL, A. J. (1937) | .. | .. | Discussion on Water Balance in Surgery by W. G. Maddock and F. A. Collier. <i>J. Amer. Med. Assoc.</i> , 108 , 6. |

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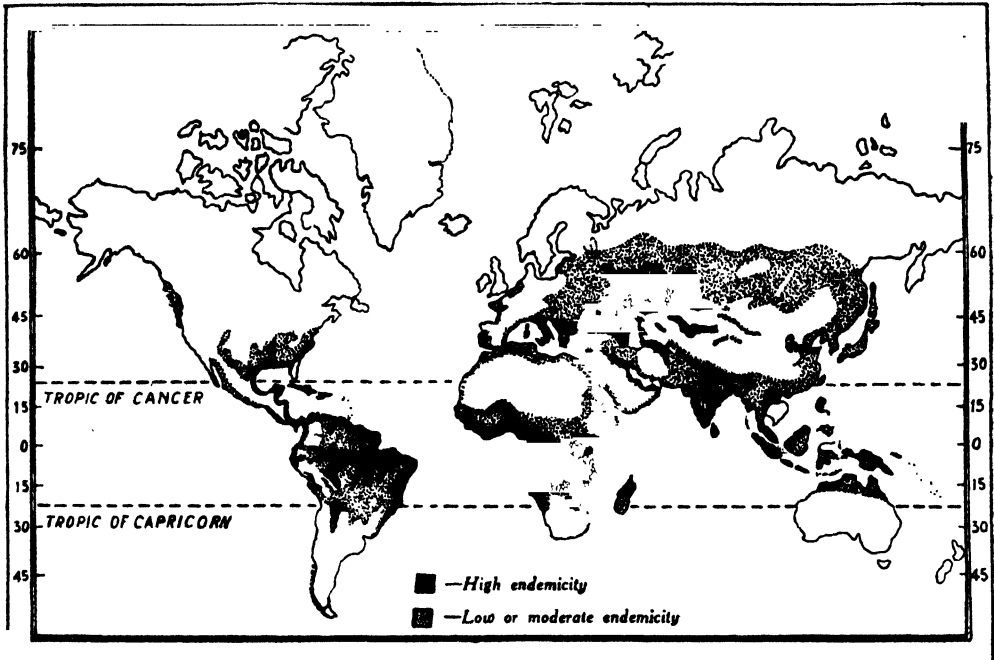
Introduction.—Malaria is by far the most important disease in the realm of tropical medicine. In the distant past it has caused the decay of empires, and in the near past the failure of the best conceived military campaigns; in our own times it has led to the abandonment of many engineering projects and has delayed innumerable others. Of all diseases except possibly the common cold, it is the most widespread, it is the cause of the greatest economic loss, and it has the highest incidence in nearly every tropical and sub-tropical country. It has been subjected to a greater amount of study than any other tropical disease and a vast amount of knowledge has been accumulated about it, yet there are many lacunæ in this knowledge; it is the most easily treated of all serious diseases, yet it is a disease in which the treatment is most often neglected; it is controllable and yet so seldom controlled; and it therefore still provides the greatest problems to the sanitarian and dominates the practice of the clinician in the tropics.

Definition.—Malaria is a febrile disease, characterized by its intermittency, amenability to treatment with the cinchona alkaloids, and by splenic enlargement; it occurs endemically and occasionally epidemically in almost every country in the world, but mainly in the tropics and sub-tropics; it is caused by a plasmodium, a protozoon of the order Hemosporidia, which is transmitted from man to man by mosquitoes of the genus *Anopheles*.

EPIDEMIOLOGY

Epidemiology means literally the science of epidemics, or it can be defined more liberally as the collection and the study of observed facts regarding the behaviour of disease in relation to man. In the case of malaria, these facts have been observed and the data regarding them collected from the time of the historian Herodotus and probably earlier, and today are still being accumulated.

Figure 4 : Distribution of malaria throughout the world.



Much of these data were collected in total ignorance of the cause of the disease and how it was transmitted from man to man; it was, however, the careful study of these accumulated facts that led, after journeys along many false trails, to the discovery of the true ætiology of malaria, and, conversely, it is our knowledge of this ætiology that has allowed us to explain many of the observed facts in its epidemiology, the reasons for which were hitherto obscure. It is therefore logical first to summarize the epidemiological data, then to state what is known about the ætiology, and finally to attempt to correlate the two and explain, as far as our present knowledge goes, what are the factors that control the incidence of malaria.

The data that have been accumulated can be arranged under a number of headings :—

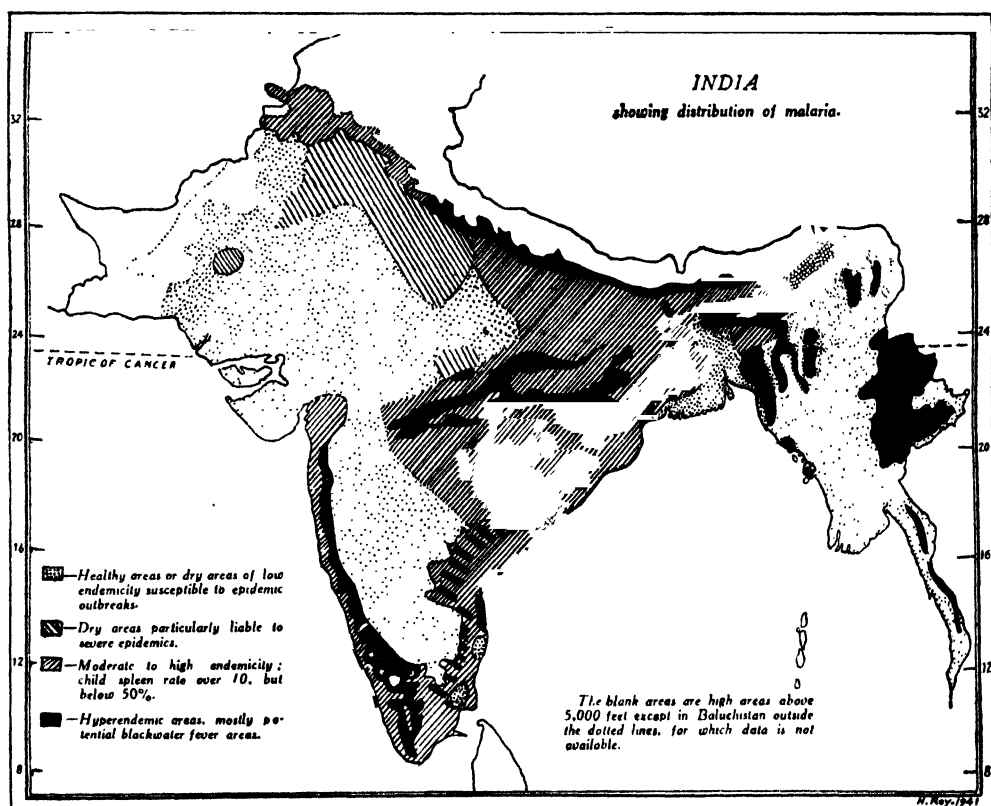
Geographical distribution.—This is world-wide; malaria occurs in the tropical, sub-tropical and temperate zones, though its incidence is higher in the former two. In these two zones malaria occurs throughout the whole populated terrain, with a few exceptions; these are that it does not occur at altitudes over 9,000 feet—in India 7,000 feet is the highest point at which it has been reported (the incidence at high altitudes is probably a matter of temperature)—and that certain islands in the Pacific, *e.g.* Tahiti, Samoa, Fiji, Hawaii, are still free from the disease; the word ‘still’ is used deliberately, because at one time other islands, Réunion, Mauritius, and until quite recently Barbados, were reported to be free from malaria.

Each of the malarial fevers caused by the four different species of parasite (*v.i.*) has a different distribution. The widest is benign tertian whose domain extends from 60°N. to 40°S.*; quartan has a patchy distribution in all three zones; but malignant tertian is essentially a malaria of warm countries, is limited by the 70°F. summer isotherm, and does not occur beyond 42°N. The malaria caused by *Plasmodium ovale* has a sparse and patchy distribution as yet ill-defined.

The world map shows that malaria occurs in almost every inhabited country on the globe. However, Scandinavia, Northern Russia and Siberia, Canada and the Northern United States, Australia except for Queensland, New Zealand, Cape Colony, and Patagonia in South America are and have always been practically free from the disease; in many parts of Great Britain and Central Europe it was at one time prevalent but has now almost disappeared. Broadly speaking, the incidence of malaria amongst the people of any country varies inversely with the distance of that country from the equator, although there are many other factors involved (figure 4).

The distribution in India and Burma is shown in figure 5.

Figure 5.



Local distribution.—In any country, district, or large area where malaria is a serious problem, there are almost always localities which are practically free from the disease; conversely, in countries in which malaria

* Beyond 45°N. and 25°S. it can scarcely be considered a disease of public health importance; there is in fact not very much inhabited land as far south as 40°.

is rare, there are localities which are intensely infected; even in a small town or village, there are often considerable differences in the malaria in different parts and one can go further and say that, in a single building, it may be found that those who live on the ground or lower floors are subject to malaria, whereas on the top floors the residents may be comparatively free. It is thus essential, when studying malaria in any locality, to note carefully where the people live who are most subject to the disease.

Observations of this kind were made in the earliest historical times. Herodotus (5th century B.C.) referred to the dangers to health of building cities near marshy country, and described how the Egyptians lived in houses built on high poles in order to avoid the damp air, that arises from the ground, and biting insects. In total ignorance of the cause of malaria, these precautions were observed by the wise rulers of those days; with all the formulated knowledge that we have at our disposal today, there are still numerous examples of how those in authority persist in placing camps and coolie lines, starting settlements, and even founding large cities in malarious countries without first consulting the malariologist, whose knowledge is based not only on the accumulated epidemiological data of some thousands of years, but on the fuller understanding of the genesis of malaria that the discoveries of the last half century have provided.

Seasonal incidence and variation from year to year.—There are few places in which malaria occurs with equal intensity throughout the year. Such variations are found even near the equator where, though there is little seasonal change in the temperature, other factors come into operation. On the whole, however, the seasonal variation in malaria is less marked the nearer one is to the equator. The seasonal incidence also depends to some extent on the malaria species that is prevalent, and where more than one species is to be found in one place, which is usually the case, the malaria may be caused mainly by one species at one time of the year and another at another time (see figure 6). Malignant tertian malaria is often called *æstivo-autumnal*, for in many European countries it only occurs in the summer and autumn, and in all countries where there is a distinct cold season, the incidence of malignant tertian drops almost to zero during this season.

Each country and even each district has its own seasonal malarial curve; in most places, this will show only minor variations from year to year, in its general shape, even though the variations in the height of the curve may be considerable.

It is usual to consider malaria as **endemic** or **epidemic**, but, even in those localities in which it is endemic, the incidence of the disease is subject to periodical exacerbations. In the epidemic regions, the epidemic does not take the form of an introduction of malaria into a place where it did

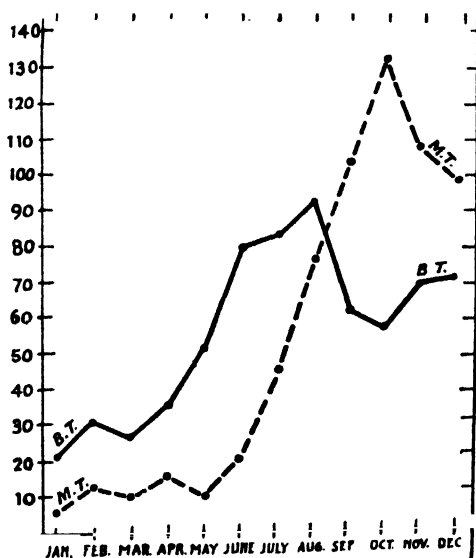


Figure 6: In June, 80 per cent of the malaria is benign tertian; in October only 30 per cent of the malaria is benign tertian (Northern India).

(Acton, H. W., 1910.)

not exist before—as is the case with cholera, for example—but of a sudden and often very dramatic flaring up of malaria in an area where it occurred in a mild form before, but was normally a disease of little public health importance during most of the year; in such an area, though the individual conditions that affect malarial incidence may not vary much from year to year, it is the concatenation of a number of events that brings about a state of affairs favourable for an epidemic, *cf.* Sydenham's epidemic constitution. Epidemics tend to occur in cycles of a definite number of years.

In India, there are two main types of malaria seasonal curve, the Punjab type and the Bengal-Assam type. In the former, the incidence is low during most of the year and with the onset of the rains there is a sudden rise which will in certain years amount to an epidemic.

These epidemics have been studied by the health authorities and it has been shown that it is often possible to foretell whether it will be a normal or bad year for malaria. This information is very valuable

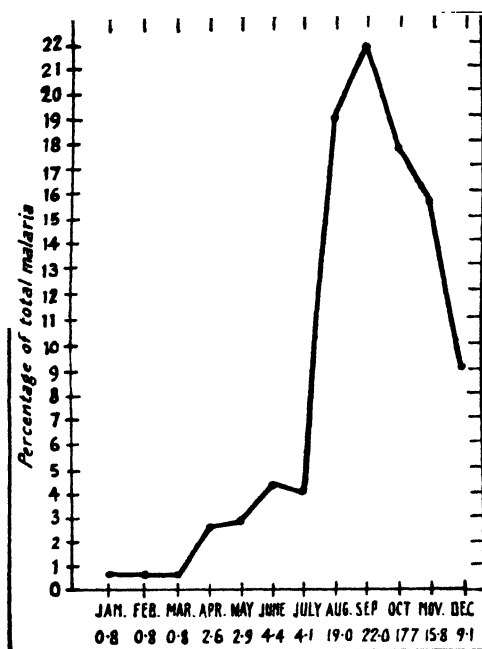


Figure 7 : Seasonal malaria curve in Delhi.

(Knowles and White, 1930.)

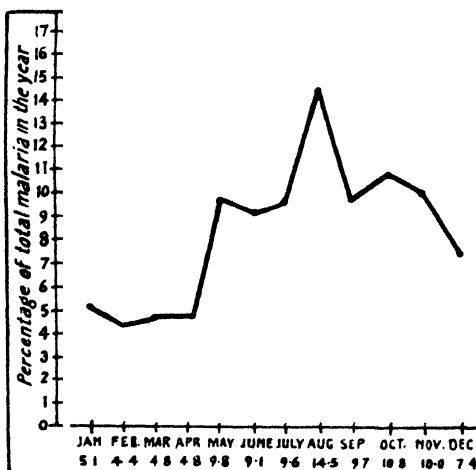


Figure 8 : Seasonal malaria curve in the Assam Valley.

(Knowles and White, 1930.)

because it enables these authorities to set in motion the special organization for dealing with the epidemic immediately it arises. In the endemic areas, *e.g.* in Assam and Bengal, the disease is perennial, but the curve shows a steady rise in July and August and reaches its peak in about November, after which it falls fairly rapidly.

A minor spring rise in the incidence curve has often been noticed, particularly in benign tertian areas in Europe.

These endemic areas are not entirely immune from epidemics, as was shown recently by the Ceylon epidemic of 1934/1935.

In studying malaria in a locality an attempt should be made to prepare a seasonal graph from past records if they are available or failing that from current observation. If possible the malaria caused by the three different species should be plotted separately. The larger the number of years included in these data the better, and if only one year, or

a small number of years, are included, an attempt should be made by careful local enquiry to ascertain if the year or years were 'normal' as far as malaria was concerned.

Age and sex incidence.—Individuals of all ages are subject to malaria. There have been a number of instances of congenital infection reported, but this is not a normal mode of transmission of the disease, it will be referred to again later. Children are particularly liable to infection, and in them it usually takes a serious form. In a malaria-infected community, children are important for two reasons; firstly, they react to malarial infection in a more standard manner than do adults, and the frequency of splenic enlargement in children is thus a valuable indication of the degree of malarial infection of a community; and, secondly, children constitute the main reservoir of infection (*vide infra*). Both sexes are equally susceptible to infection and there is seldom any difference in the sex incidences of the disease.

The age composition of a community is thus an important factor in normal epidemiology. If children form a large proportion of the population malaria will be more difficult to control.

Race and caste.—Persons of all races seem to be equally susceptible to infection, provided the circumstances in which they live are the same, though there are considerable individual variations in susceptibility. The morbidity caused by malaria does, however, vary considerably, and there are many instances in which the members of the indigenous races appear to be unaffected by the disease, whereas foreigners, of whatever race, become seriously ill when infected; one of the best examples of this is provided by blackwater fever, a malarial disease (*vide infra*). It has also frequently been observed that any disturbance of the population, for example, the migration of a large number of persons into another country, may not only lead to a high incidence of malaria amongst the immigrants, but also to a great exacerbation of the disease amongst the indigenous inhabitants. This is a recognized principle of herd immunity that is certainly applicable to malaria.

The racial composition of a population and more especially any changes that have taken place recently are therefore important facts to be noted.

Occupation, habits, and economic status.—Numerous observations have been made under this heading, back to the time of the Roman historians who pointed out that in certain malarious districts it was dangerous to walk out at night and loiter by the water's edge. The danger to soldiers carrying out night operations or standing guard at night, and to police on night duty has frequently been observed. Again, the soldier, previously infected, who has to make long marches in trying circumstances is very liable to suffer from malaria, either an initial attack or a relapse. Any severe physical strain or trauma, *e.g.* surgical or obstetric operations, x-ray applications to the spleen, or sudden cold, may precipitate an attack in an infected subject.

The economic factor is one of great importance in determining the development of immunity to malaria. It has been shown frequently that when the economic condition, of a rural population in particular, improves the malaria loses much of its morbid potentialities. Conversely, severe epidemics have often been correlated with an economic depression.

The best example is the Roman Campagna which, once harbouring a flourishing agricultural community, was through misgovernment allowed to degenerate at intervals into a deadly malarious swamp for nearly two thousand years, but has now reacquired its former agricultural prosperity and malaria has almost disappeared*. Other examples of how development and prosperity have banished malaria are the fen districts in England, the low countries in Holland and Germany, Lower Egypt, and in India the deltas of the Cauvery and the Godavari. Conversely, Corsica is often quoted as a country in which agricultural deterioration has led to a great increase of malaria, and the Ceylon epidemic followed a period of economic depression.

It is thus obviously important to collect full data under all these headings.

ÆTIOLOGY

Historical.—The early theories regarding the cause of malaria were numerous. The word 'mal-aria' (bad air) is evidence of one of the earlier theories, not unreasonably founded on the fact that the disease prevailed in low marshy country where the 'poisonous miasma' arose from the ground at night. Another theory was connected with water, and it has been suggested that the first Roman aqueducts were built on account of the prevalence of fever in Rome; the partial success of this measure would be accounted for by the reduction of other, water-borne fevers.

Night-flying biting insects came under suspicion very frequently, and Herodotus referred to the use of, what we should call, mosquito nets by the Egyptians.

Laveran described the malaria parasite in 1880; this discovery was developed considerably by the Italian workers, Marchiafava, Celli, and Golgi, who demonstrated the different species and associated these with the various clinical pictures. This work was hampered by the absence of a suitable stain for the parasites, and the perfection of a staining technique by Romanowsky in 1891 considerably aided future investigations.

This discovery of the causal organism opened up the field for the investigation into the mode of transmission of this parasite from man to man. It is difficult to trace the germ of an idea to its origin. Credit is due to the Jules Vernes and H. G. Wellses of medical science, who produce many excellent and also, it should be remembered, many false ideas. It is, however, the man who has the perspicacity to sort the grain from the chaff (or who, the cynics will say, is lucky enough to follow the right trail) and develops the ideas, that usually gets, and probably deserves, the most credit. When Manson first turned his attention to the problem of the transmission of malaria, the idea of an arthropod carrying a disease was new, but not entirely new, for as back as 1869 Fedtschenko suggested that dracontiasis was transmitted through the medium of cyclops (an

* The association between malaria and poverty cannot be questioned. It has been assumed by nearly every malariologist that malnutrition causes malaria whilst at the same time it has been appreciated that malaria also causes poverty, with its sequel, malnutrition; in fact, that there is a vicious circle.

Hackett (1937) has questioned whether malnutrition does cause malaria and adopts the view that the reaction is all in one direction, namely, malaria causing poverty and malnutrition. This view is supported by Covell (private communications).

In support of this view, these very widely experienced malariologists quote much suggestive data including the fact that the healthy and well-fed British soldier is very susceptible to malaria which in him quite often takes a fatal course.

This and most of the other examples they quote do not in any way run counter to the views of the writer regarding malnutrition and malaria; he believes, from medical and pathological as well as from epidemiological experience, that nutrition affects, not the non-immune patient's immediate response to a malarial attack, but rather the way that immunity develops in the individual subjected to repeated attacks of malaria.

observation subsequently shown to be correct). Ten years later, Manson discovered filarial embryos in the mosquito, and from this time onwards he probably nursed the idea that malaria was also in some way connected with the mosquito. In 1883 King in America published a paper containing a well-reasoned justification for the mosquito hypothesis. Manson interested Ronald Ross in this subject and in 1897, working in Secunderabad, Ross discovered the pigmented bodies (oöcysts) in the stomach wall of the dapple-winged (anopheles) mosquito, previously fed on a patient suffering from malaria. In the following year, working in a small laboratory in the Presidency General Hospital in Calcutta, he demonstrated the cycle of *Proteosoma*, a parasite that infects sparrows and is in many ways comparable to the malarial parasite in man, in culex mosquitoes. Later in the same year, Bignami, Grassi, and Bastianelli demonstrated the plasmodium cycle in anopheles and man. Finally, in 1900, Manson staged a human experiment in which infected mosquitoes were taken to England and in a malaria-free locality allowed to feed on volunteers, who subsequently developed malaria. Subsequent work by thousands of investigators in nearly every country in the world has shown which species of mosquito carry malaria and which do not.

The causal organism.—This is a protozoal parasite of the class Sporozoa, the order Hæmosporidia, and the genus *Plasmodium*. There are four recognized* species of *Plasmodium* that infect man in nature, *Plasmodium falciparum* that causes malignant tertian malaria, *P. malariae* that causes quartan malaria, *P. vivax* that causes benign tertian, and *P. ovale* that causes a particularly mild form of malaria. (The monkey malarial parasite, *P. knowlesi*, can be artificially established in man and causes transient malaria, but it is doubtful if this occurs in nature.)

There are undoubtedly a large number of 'strains' of parasites of each species. These strains whilst being morphologically identical exhibit certain characteristics which breed true to type. In England, for example, where a number of different strains are maintained for therapeutic purposes, malaria induced by infection with the Roumanian strain differs from that induced by infection with the Madagascar strain; and the Rome strain of malignant tertian is particularly resistant to treatment.

In one locality there are probably many strains; this is indicated by the fact that, in a very malarious place, it may be many years before the children acquire immunity to all the malarial strains in the locality.

The life cycles of the four species of human plasmodium are practically the same.

There are two phases in the life of the malaria parasite, an intra-corporeal phase in the intermediate host—man, and an extra-corporeal phase in the definitive host—the female mosquito, and two cycles, the asexual and the sexual. These phases and cycles do not correspond with each other.

The forms of the malaria parasite that are found in man.—The ring form, which is seen in a Romanowsky-stained film as a pale blue disc with a red chromatin dot at the edge lying within a red blood corpuscle, is at first very small but rapidly increases in size, becomes amœboid, secretes a dark pigment (hæmozoin), and eventually develops into a schizont which fills practically the whole red cell; the schizont has the same pale blue cytoplasm, its chromatin is split up, and the hæmozoin pigment collects into masses; the fragments of chromatin which are more or less equal in size now tend to become arranged evenly throughout the cytoplasm and

* *P. tenue* is probably a valid species, but it is little more than a protozoological curiosity. *P. perniciosum*, on the other hand, may turn out to be important; it is the name given to a small strain of *P. falciparum* which has been found in South America and elsewhere, and is reported to cause a particularly virulent form of malaria.

the pigment tends to aggregate into one solid mass, the stage which is known as the **rosette**; the rosette bursts and releases into the circulation the **merozoites**, small ovoid or globular bodies consisting of pale blue cytoplasm and red chromatin nuclei, the hæmozoin pigment, and the debris of the containing red cell. The number of merozoites that the rosette contains varies with the species; in *P. malariae* there are from 8 to 12, in *P. vivax* from 14 to 24, and in *P. falciparum* the number is more variable, from 12 to 32. The merozoites then attach themselves to and eventually enter red cells where they again start the **asexual** cycle, or they may develop into **sexual** forms, the male and the female gametocytes. The fully-developed gametocyte fills the whole cell like the schizont, but the gametocytes of the three malaria species have distinctive characteristics. The most distinctive is the crescent form of the malignant tertian parasite; the male gametocyte is long and slender with a large nucleus and the pigment scattered throughout the cytoplasm, whereas the female is stouter and shorter, and has a small nucleus with the pigment distributed around it. The *P. vivax* tertian and *P. malariae* gametocytes are more or less globular; in the former the nucleus is an irregular mass, and in the latter it takes the form of a rod or band. (Further details of the morphology of the different species will be given below; see DIAGNOSIS.)

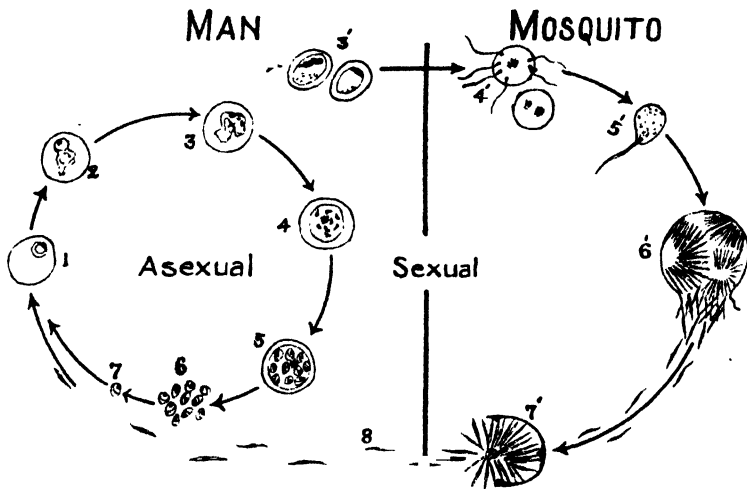


Figure 9.

Asexual cycle

- 1 Ring form.
- 2 Growing trophozoite.
- 3 Trophozoite.
- 4 Schizont.
- 5 Fully-grown schizont-rosette form.
- 6 Burst rosette.
- 7 Merozoites.

Sexual cycle

- 1 Ring form.
- 2 Growing trophozoite.
- 3' Gametocytes ♂ and ♀
- 4' Flagellate bodies and gametocyte ♀
- 5' Fertilized gamete. (Oökinete not shown.)
- 6' Oöcyst—in stomach in mosquitoes.
- 7' Sporozoites—in salivary gland.
- 8 Free sporozoites.

The asexual cycle.—The cycle—ring, schizont, rosette, merozoite, and again ring—lasts 48 hours in malignant tertian and in benign tertian, and 72 hours in quartan malaria. This fact determines the periodicity of the fever; the rigor corresponds to the bursting of the rosette. This asexual

cycle leads to the multiplication of the parasites within the host, but, if it were the only form of development, there would be no chance of propagation of the species beyond this individual host, for the particular parasitic brood would end its existence in this host; they might kill him, or they might be destroyed by the cellular or humoral reactions of the host's tissues; therefore, for the continuance of the parasite's existence the sexual phase is necessary (*see figure 9*).

On the other hand, the sexual parasites, the gametocytes, have no future within the individual host in which they are formed, for they are capable of no further development. Their future lies only in the mosquito, and if they are not taken up by a suitable mosquito, after living for about three weeks in the blood of their host, they die.

The sexual cycle.—When a mosquito vector feeds on an infected man, it takes in a number of malaria parasites. Any asexual forms will die, but the mature male and female gametocytes continue to develop in the stomach of the mosquito; from the male gametocyte a number of flagellate bodies separate and eventually enter a female gametocyte which they fertilize; the fertilized gametocyte, or gamete, undergoes development and becomes an **ookinete** an elongated body with considerable powers of penetration. The ookinete penetrates the endothelial lining and buries itself in the wall of the mosquito's stomach, where it develops into an **oocyst**. These oöcysts can be seen easily, under a dissecting microscope, as round glistening bodies in the wall of the dissected mosquito's stomach; they are 40 to 80 μ in size. They eventually burst, releasing a large number of **sporozoites** into the body cavity of the mosquito. The sporozoites are motile bodies and find their way into every part of the body of the mosquito, except the ovaries, but in the salivary glands they find a particularly suitable medium for continuing their existence. Once the sporozoites have reached the salivary glands, whenever the mosquito takes a blood meal the sporozoites escape with the salivary material and enter the body of their new host.

The time taken in this phase in the mosquito is variable, according to the conditions; the shortest time is probably about 8 days, but under adverse conditions, particularly in the cold when the mosquito is hibernating, it may take many months. The average time in moderately favourable circumstances is usually looked upon as about 12 days.

It was at one time thought that a certain minimum number of gametocytes had to be present in the blood before the mosquito would become infected; this number was placed at 12 by Darling (1909). Recent work has shown that there are many other factors besides the number of gametocytes that determine infection of the mosquito; these include species and strain of plasmodium, and species and individual variability of mosquito, some individuals of recognized vector species being entirely refractory to infection.

Ability to transmit infection starts to decline about ten days after the mosquito first becomes infective and after 40 to 50 days it usually ceases to be infective (Boyd and Stratman-Thomas, 1934; Boyd *et al.*, 1936), unless meanwhile it has again fed on a malarial patient. James (1926), however, reported an instance in which mosquitoes kept at a low temperature remained infective for 92 days.

Development only takes place in the *female* mosquito.

There is considerable uncertainty as to exactly what happens to the sporozoite when it enters man. A few facts are known; it does not, for example, remain in the blood stream, for blood taken during the first eight days is not infective. On analogy with observations made in birds it is thought that the parasite enters certain reticulo-endothelial cells of the host and undergoes development there. After this latent period, the malaria parasite reappears in the peripheral blood as a ring form; it then completes a number of asexual cycles and may again become a gametocyte.

The term 'mosquito cycle' is sometimes used, but actually there is no *cycle* in the mosquito. The parasites enter the mosquito as gametocytes and leave it as sporozoites. From a pair of gametocytes a very large number of sporozoites are formed and it is almost certainly by weight of numbers of sporozoites formed from the primary infection that the mosquito remains infective for a long time, and not through multiplication of the sporozoites, as Missiroli has suggested, though under artificial conditions mosquitoes have been known to remain infective and to be capable of transmitting malaria for over 90 days. The sexual *cycle* is only completed when gametocytes are again formed; thus both the mosquito and man are essential for this cycle to take place. The average period of the sexual cycle is at least a month; this is made up by about 12 days' development in the mosquito, about 12 days' incubation period in man, and, say another six days from the time the infection reaches the clinical 'threshold' to the appearance of gametocytes; these figures are not minimal, but probably represent a low average.

The essentials for the natural transmission of malaria and the factors influencing them.—

The essentials are :—

- A. *The malaria parasite.*
- B. *The mosquito vector.*
- C. *Man.*
- D. *The links between B and C; i.e. the lines of communication along which the parasite travels.*

In the absence of any one of these essentials, malaria will not exist. If the conditions influencing all these four essentials favour malariogenesis, the incidence of malaria will be maximal; if conditions influencing *any* of them are unfavourable, malaria incidence will be sub-maximal; and if conditions influencing *all* of them are unfavourable, malaria will be minimal, or may not occur.

It is by the study of the various climatic and other terrestrial factors that influence these four essentials that we shall understand and explain the observed facts regarding the incidence, distribution, etc., of malaria, which we have recorded and which we know as the epidemiology of the disease.

This is not however an academic study for it is only by knowing what these malariogenic factors are and how they exert their influence that we can hope to eliminate, reduce, or avoid these influences. The study of how this has been and is being done, how it can be done, and how it might be done, constitute the science of malariology, even the essentials of which would fill a large volume; here it is only possible to give the barest outline.

The malariogenic factors are conveniently grouped under these four headings :—

A. The malaria parasite.—As a very large proportion of the human race has been or is infected with some species of malaria parasite, it is very unlikely that a community exists where the other three essentials are present, and yet there are no malaria parasites; such a state of affairs is conceivable (and has a parallel in another disease, *i.e.* yellow fever), and, as long as no infected man or mosquito was introduced, the community would remain free from malaria.

However, apart from these theoretical considerations, the parasite factor is an important one, and malaria in any locality will be influenced largely by the number and immunological variety of the strains of malaria parasite present. Further, it has been shown that other conditions remaining unchanged, new strains of malaria parasite introduced into a community by immigration of foreigners, importation of foreign labour, etc. (*vide supra*), will cause a sharp rise in the incidence of malaria in that community.

Again, the proximity of the reservoirs of malarial infection will be an important factor in determining the incidence in a locality.

The parasite has two phases and the factors that influence it will be different in each case.

In the *mosquito*, it is affected by temperature; if this is not favourable, the development of the malaria parasite will be arrested, though the mosquito may continue to flourish. In certain sub-optimal conditions development only takes place up to the oöcyst stage. A temperature of 60°F. and a humidity of 63 per cent (to ensure longevity of the mosquito) are necessary for the development of *P. falciparum*: this explains the absence of malignant tertian malaria from cold countries, its autumn periodicity in temperate countries, and in hot countries its disappearance during periods of very high temperature but low humidity.

Other possibilities that have not yet been fully explored are the existence of other parasitic infections in the mosquito and the nature of its food, for mosquitoes take other fluids besides their blood meals.

In *man*, the parasite is influenced by the host's natural and acquired immunity (*vide infra*).

Another factor is the formation of gametocytes. It has been suggested that this is a phenomenon of immunity, but this is quite obviously not the case, for infants who enjoy the least immunity are the greatest gametocyte producers. If therefore any correlation between gametocyte formation and immunity exists, it is a negative one.

For transmission to occur there must be gametocytes in the peripheral blood; their presence, quantitatively considered, is therefore an important factor in malariogenesis.

Finally, the effects of therapy have to be considered under this heading; any drug that destroys gametocytes directly or indirectly is capable of influencing malarial endemicity.

B. The mosquito vector.—Not all mosquitoes carry malaria, only certain species. The delay in incriminating the mosquito in the ætiology of malaria was undoubtedly due to the lack of basic entomological knowledge. The existence of different species of mosquitoes was recognized but little attention had been paid to the subject; however, the amount of knowledge that has been accumulated in the last 50 years is enormous, and this

particular aspect of the science of malariology has now probably received more attention than any other, but knowledge on the differentiation of species is still incomplete, and apparently homogeneous species, e.g. *A. maculipennis* in Europe, are frequently being shown to be made up of several heterogeneous sub-species, as our methods of identification improve. Three are at least 1,400 recognized species of mosquito (Edwards, 1932), and even the anopheline species in India alone number over fifty. All the mosquito vectors belong to the genus *Anopheles*, but all *anopheles* are not vectors. The most important vectors in different countries are:—

In Europe	..	<i>A. maculipennis</i> group, <i>superpictus</i> , <i>sergenti</i> and <i>claviger</i> .
India and Ceylon	..	<i>A. culicifacies</i> , <i>philippinensis</i> group, <i>fluvialilis</i> , <i>minimus</i> , <i>superpictus</i> , <i>sundaicus</i> and <i>stephensi</i> .
Palestine and Syria	..	<i>A. elutus</i> and <i>superpictus</i> .
Iraq and Iran	..	<i>A. elutus</i> , <i>superpictus</i> and <i>stephensi</i> .
China	..	<i>A. minimus</i> , <i>hyrcanus</i> and <i>maculipennis</i> group.
Burma and Siam	..	<i>A. minimus</i> and <i>sundaicus</i> .
Malaya	..	<i>A. maculatus</i> , <i>umbrosus</i> , <i>sundaicus</i> , <i>aconitus</i> and <i>hyrcanus</i> .
Egypt	..	<i>A. pharoensis</i> .
Africa	..	<i>A. gambiae</i> and <i>funestus</i> .
Australasia	..	<i>A. punctulatus</i> group, <i>amictus</i> and <i>barbirostris</i> .
America	..	<i>A. quadrimaculatus</i> , <i>crucians</i> , <i>maculipennis</i> , <i>punctimacula</i> , <i>pseudo-punctipennis</i> , <i>darlingi</i> , <i>albimanus</i> , <i>albitalis</i> and recently <i>gambiae</i> .

All potential vectors are not of importance as vectors in nature; nor are apparently identical species of equal importance as vectors in all localities in which they are found, e.g. *A. subpictus* carries malaria in New Guinea, but, though the Bengal species can be infected in the laboratory, in nature it is never found infected, apparently because it is a delicate species and does not survive long.

The life cycle of the mosquito.—This is similar to that of all nematocera. The adult mosquito, or imago, lays its eggs on a water surface where they float (figure 10: 1a and 1b). From the ovum a larva hatches out which feeds on algæ and other organic matter. It also requires air, so that it has continually to come to the surface and normally rests just below the surface with its spiracles in contact with the air (figure 10: 2a and 2b). The larva after several moults changes into a pupa (figure 10: 3a and 3b) which does not require food. Finally, from the pupa the imago, or adult mosquito (figure 10: 4a and 4b), emerges. Thus, for development of ovum to adult, water is necessary.

The adult mosquito lives on fruit and plant juices, but the female requires a blood meal for the maturation of its eggs. This need not necessarily be human or even mammalian blood, but may be avian or reptilian. Most mosquito vectors are night feeders. The distance of dispersion of the mosquito is a subject that has been studied very frequently and there are experimental data about many species. Normally, the mosquito does not fly far from its breeding place, or its food. Some species are particularly domestic and never stray more than a hundred yards or so from the locality where they breed and find their food (e.g. *Aedes ægypti*). However, some mosquitoes will fly many miles 'down wind', and it must be remembered that for them to transmit malaria they do not have to fly back to their breeding place. The writer recently had the experience of malaria-infected mosquitoes (*A. gambiae* or *A. funestus*) being blown a distance of well over a mile from a malarious shore into a ship. The normal range of malaria-carrying mosquitoes is under a mile.

The time taken to complete the life cycle of the mosquito varies according to the conditions, and is mainly controlled by temperature. Under optimum conditions development from ovum to imago may be completed in as short a time as five days, but this is probably exceptional. In southern Europe, the full cycle takes about a month even in summer, and in colder countries, it is much slower, and may be arrested for many months. Wintering will occur at the egg, larva, or adult stages, according

to the species. Similarly, the length of life of the adult mosquito varies considerably; in cold climates where it undergoes periods of hibernation, it will live up to nine months, but in the tropics, where metabolism is speeded

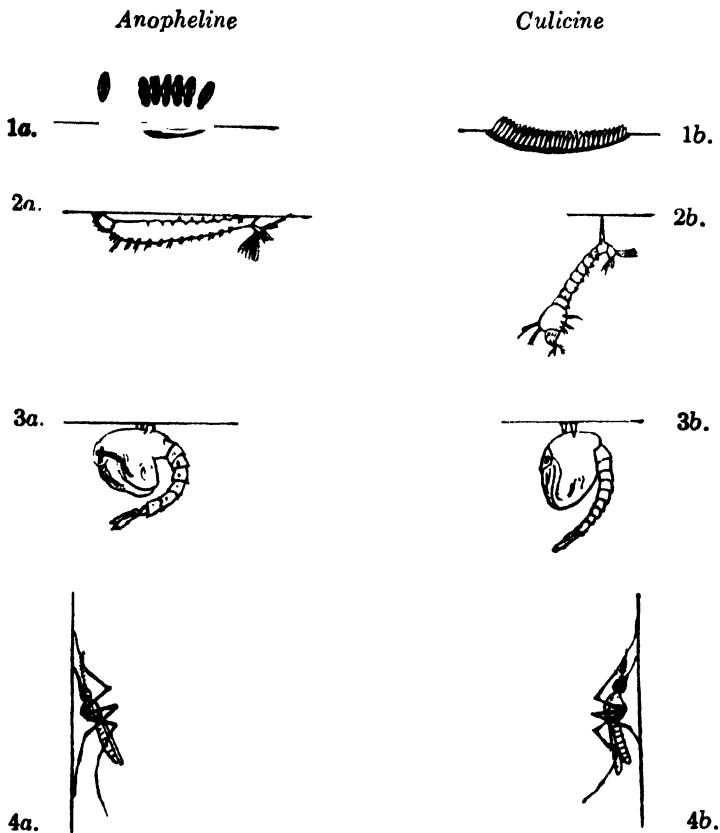


Figure 10.

- | <i>Anopheline</i> | <i>Culicine</i> |
|---|--|
| 1a. Eggs with floats : also shows how they float. | 1b. Eggs and float. |
| 2a. Larva : floats horizontally on the water surface. | 2b. Larva : hanging from water surface. |
| 3a. Pupa : breathing trumpets funnel-shaped. | 3b. Pupa : breathing trumpets long and narrow. |
| 4a. Imago : body straight. | 4b. Imago : hunch-backed. |

up, its average life span is probably less than a month. In nature, the mosquito is subject to many adverse influences, infections, ecto-parasites, and innumerable natural enemies, fish in the water, bats in the air, and lizards on the wall, so, though it is extremely fertile, its life is a precarious one; this is an important factor and explains the relatively low sporozoite infection rate amongst mosquitoes caught in nature even in a highly malarious locality.

With this complicated life cycle it will be obvious that the factors that influence the mosquito will be numerous; these include temperature, humidity, rainfall, sub-soil water level, the nature of the water, the nature of the soil, physiological conditions, both natural and man-

made; altitude (mainly in its relation to temperature), vegetation, biological competition, and natural enemies.

When these conditions are very unfavourable mosquitoes will be reduced to a minimum, or they may be absent altogether and malaria will not occur, but there are places where the conditions are extremely favourable and yet no mosquitoes of the vector species exist, *e.g.* certain isolated Pacific islands into which the mosquito vectors have never been introduced and which are therefore free from malaria. In the past, there were other such islands, but into these mosquitoes were introduced and malaria is now endemic (*vide supra*).

Many instances have been observed in which fresh vector species have been introduced into a country or district, and have caused a considerable increase in malaria; perhaps the best recent example is the introduction from Africa of *A. gambiae*—possibly to some extent by the trans-Atlantic plane service—into South America, where it has caused a most disastrous increase in malaria.

It is impossible to summarize the effects of these various factors, or to make any dogmatic statements, such as, for example, that rainfall is favourable to mosquitoes, for it may be just the reverse, and there are many circumstances in which rainfall will actually stop malarial incidence; or that abundant vegetation favours the mosquito and malarial incidence, for there are some vector species that disappear when streams are shaded (*Anopheles minimus*), though others (*A. umbrosus*) require shade; some mosquitoes flourish only in clear water, others are less particular and seem to prefer contaminated water, yet others need a degree of salinity (*A. sudaicus*); some prefer stagnant pools, others running water; and so on. It does not mean that, because this information cannot be summarized, our knowledge on these subjects is confused and unsatisfactory. On the contrary, there is a very great deal of accurate and detailed information on the habits of most of the important vector species. It is a matter of primary importance that anyone who has any responsibility in the matter of malaria control should find out first what are the local vector species and the relative importance of each; he should then ascertain from the numerous books and other publications on malariology what are the habits of the most important of these; and finally by observation he should find out if in his locality they conform to their normal behaviour. There are examples of apparently identical species behaving differently in different countries [*e.g.* *A. fluviatilis* feeds exclusively on man in the Wynaad and Nilgiris (South India) and is a potent vector, whereas in the Himalayan foot-hills it feeds exclusively on cattle and is of practically no importance as a vector], but such instances are rare, and the instances in which *in nature* they have been made to change their habits (*e.g.* to breed in fresh water when they have been deprived of saline water) are even rarer. It will usually be found that *one species only is of real importance* and this will facilitate control very considerably.

C. Man.—The influence of the human factor in the determination of malarial incidence has been to some extent neglected since the day when attention was first attracted to the parasite and the mosquito.

For all practical purposes, man is the only intermediate host of the malaria species with which we are now concerned, though in certain jungle areas a higher mosquito-infection rate than appears to be explainable on the grounds of the very sparse human population has led to the suggestion that apes may be the source of infection. There are of course many other plasmodia besides the four 'human' species, and man has been infected with the monkey plasmodium, *P. knowlesi*, under artificial conditions.

The important factors under this heading are : the density and age composition of the population, the previous malarial experience of the community as a whole or of the different groups that compose a community, the climatic conditions under which they live, their economic status and general mode of life, and their general state of health and nutrition.

Man enjoys both natural and acquired immunity to malarial infection.

There is probably no such thing as complete **natural immunity** to all strains of the four plasmodial species that commonly infect man, although man does enjoy immunity from infection by certain simian plasmodia; there is however incomplete immunity, for it is often difficult to infect a man with malaria and there are the many instances when the malaria has not developed for some years, until the host has been subjected to cold or some physical strain and his natural resistance thereby lowered.

There is as yet no agreement on the nature of **acquired immunity**. There is little doubt that some, both cellular and humoral, immunity is acquired, and that it is a strain-specific immunity and to a much less extent a general immunity for all malaria strains. The other explanations for the comparative freedom of certain people from malaria is that all those who did not enjoy some natural immunity were killed off in their infancy, or that the apparent immunity is really a 'premunity', that is to say, the individual is already infected with malaria so that his body defences are active and prevent super-infection, which, some might argue, constitutes immunity.

The effect of acquired immunity is well demonstrated in highly endemic localities, where infants and young children show the highest infection rate, often amounting to 100 per cent, and suffer almost continuously from fever; the average number of parasites in their peripheral blood may amount to 10,000 or more per c.mm. Adults in the same locality will also show a high infection rate, though short of 100 per cent, but the average number of parasites will be far less, amounting to perhaps one-hundredth that in the infants, and they will only suffer from occasional febrile attacks. Christophers (1925) has shown that, under these conditions, the infection rate, the parasite count and the frequency of the febrile attacks show a steady decline as the age advances.

There is however no doubt that this immunity is very labile, and that when the general powers of resistance of the host are lowered for any reason, for example, by famine and hardships, as well as by fatigue and cold, mentioned above, he is far more susceptible to malarial morbidity, even if not to malaria infection.

Conversely, when they are raised by good food and comfortable living conditions, he will be much less liable to malarial morbidity and probably to malaria infection.

Thus, immunity is important to the individual, but even more important to the community, for the rise in immunity means a reduction in the circulating parasites and therefore in the source of infection to others. Conversely, a bad general breakdown in immunity, from any cause, will lead to a vicious circle of increased infection and increased morbidity; sudden disastrous epidemics that sometimes occur even in endemic areas are explainable in this way.

The presence of children in a community will increase incidence both on account of the heavy infections that they suffer as a result of their low immunity, and because they produce large numbers of gametocytes.

The introduction of a number of non-immunes—either non-immune to all malaria strains or to the local strains—into a malarious community will be like adding fuel to a smouldering fire, and will increase malaria incidence in the whole community.

D. The links between man and the mosquito.—Both man and the mosquito are essential but if they could be kept apart malaria would die out. The stronger the links, the higher the malaria incidence, and *vice versa*. The important factors can be considered under two headings, (i) general and (ii) local and personal.

(i) The **general** factors include density of human population, density of mosquito vector population, living conditions of the population, and movements of the population, air movements and prevailing winds, and animal deviation (zoophilism).

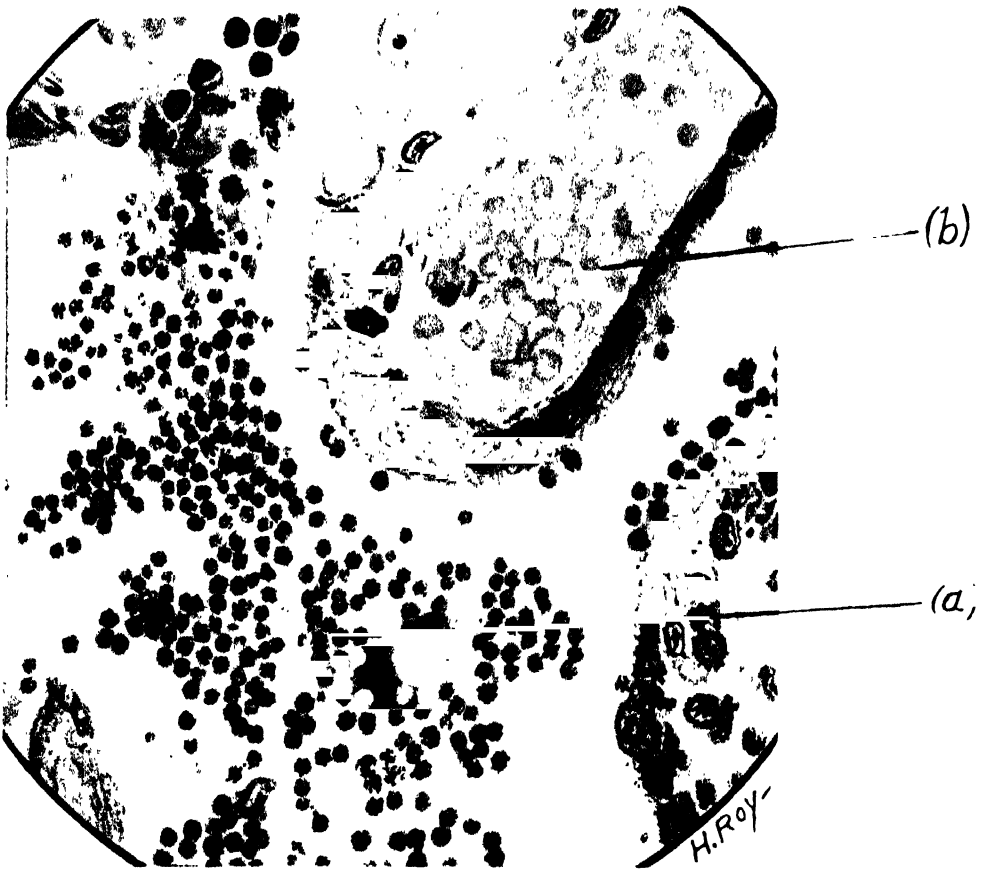
This question of the densities of the human and mosquito populations and malaria incidence is a mathematical problem, but it is not an entirely simple one. On the whole, the denser the populations the greater are the chances of contact between man and the mosquito, but this would seem to suggest that the disease should be more prevalent in towns, whereas we know that it is not. The reason for this is that in towns the density of the human population is more than counterbalanced by the sparsity of the mosquito population.

Again, it must be remembered that to transmit malaria the mosquito must take at least two human blood feeds; there are many factors which militate against the chance of this occurring, for example, the high mortality amongst mosquitoes in nature, which means a short survival period for each individual mosquito; this cannot be entirely compensated by a higher propagation rate which would only mean that a larger number of mosquitoes took a single blood meal. Here also the effect of wind will come in, for after taking the infecting feed the mosquitoes, which are very susceptible to wind currents though they are capable of flight against the wind, may be blown away from their source of human blood meals.

The chance of contact between man and mosquito will also vary considerably with differences in the **living habits of the population**. If the people are poor and live in dark ill-ventilated huts, mosquitoes will remain in the corners of the huts during the day and emerge at night to feed almost uninterruptedly on their human hosts; under these conditions the chances of transmission will be enormous. On the other hand, if the people are well-to-do and live in well-lighted and well-ventilated houses with electric fans, though mosquitoes may come in at night, they will have fewer places to rest during the day, will be driven out of the house, have to face greater dangers outside, and (individually) will probably not return; in these circumstances there is considerable dilution of the once-fed mosquitoes and the chances of a second feed being taken are considerably reduced. If in addition protective measures are used by the people, the chances are reduced still further, but this is a personal matter and will be considered below.

Zoophilism or animal deviation is undoubtedly an important factor although there are different schools of thought on this subject. The original view expressed by Roubaud was that the proximity of cattle deflected mosquitoes from their human hosts, but the evidence on the subject has been confusing and it is obvious that in some circumstances cattle attract mosquitoes to their vicinity and thereby favour malaria transmission amongst the people living in close association with them. The fact that some species that are known as potential vectors and yet are

PLATE III



A. Section of the placenta of a *Silenus rhesus* monkey. Note (a) the intervillous spaces, containing maternal blood with 90 per cent of the red cells infected with *Plasmodium knowlesi*, and (b) the blood vessel of a chorionic villus containing uninfected fetal red cells. Drawing with an Abbé camera lucida; approximately $\times 790$ magnification. (Das Gupta, 1939.)

B. The spleen in severe malignant tertian (*Plasmodium falciparum*)

never found infected in nature may be explained by their zoöphilic habits. Some species of mosquito vector are anthropophilic whilst others are zoöphilic.

Strictly speaking, the word 'zoöphilic' should be applied only to species that feed on cattle exclusively. Anthropophilic is applied to species that are indifferent and will feed on either cattle or man but with a varying degree of preference for the former; these include the most important vector species. It is doubtful if there are any species that have a real preference for human blood; Covell thinks that possibly *A. minimus* and *A. fluviatilis* in Southern India may be placed in this category.

The precipitin test for the identification of blood meals in insects was used by the writer and his co-workers (Lloyd, Napier and Smith) as long ago as 1925 in studying the part played by sandflies in the epidemiology of kala-azar, but it is only during the last few years that the method has been used to any extent by malariologists; valuable information regarding the feeding habits of different species should be obtained from such studies.

(ii) The local and personal factors are, position and height of residence, personal habits and clothing, and care in the use of artificial means of protection.

The ancient Egyptians built their houses on tall poles, and the writer lived on the fifth floor of a block of flats; both thereby avoided mosquitoes and malaria. Whether a residence is near a mosquito breeding ground is obviously a matter of prime importance, and here again the direction of the prevailing wind is important. The careful individual who keeps his house mosquito-proof, or uses efficient mosquito nets and protects himself and his family by suitable clothing or the use of repellents, will run less chance of contracting malaria than the careless and happy-go-lucky one.

Congenital transmission.—This does not occur normally, even when the mother has a heavy infection; sections have been cut showing the uterine blood sinuses containing numerous parasites and the contiguous placental sinuses entirely free. When direct infection of the foetus does take place, it is probably the result of some accidental breach in the dividing membrane. Strickland and Baird (1939) recently reported six instances of infants seven days or less old showing parasites in their blood; in one instance they were found within 15 hours of birth. These six cases had been encountered in the latter's practice in a period of 2½ years. Many other individual instances have been reported.

Das Gupta (1939) however showed that, in a pregnant monkey infected with *Plasmodium knowlesi*, though the maternal circulation showed enormous numbers of plasmodia, the foetal side of the placenta showed none (see Plate III).

Artificial means by which malaria may be transmitted.—The deliberate induction of malaria is a method of treatment now recognized as of value in certain mental and nervous diseases; this is known as malaria therapy. The methods adopted are: (a) the quasi-naturalistic method, allowing an infected mosquito to feed on the patient, (b) a modification of this method, dissecting the infected mosquito and injecting the sporozoites into the patient, and (c) by inoculating the blood taken from a patient suffering from malaria. The disadvantage of the third method is that one may also transmit other diseases, e.g. syphilis. The quasi-naturalistic methods

reduce the chances of, but do not preclude, the transmission of a mixed infection, for example, malignant as well as benign tertian infection. A further reference will be made to this subject (see p. 121).

Blood transfusion provides another means by which transmission may occur. The danger of transmission occurring this way in tropical practice is very considerable and presents a serious problem. One way of avoiding this danger is to use plasma whenever possible. A very careful medical history of the donor will probably be even more useful than a blood-smear examination, which is an obvious precaution that should always be taken before using blood for transfusion, but neither of these precautions will be sufficient to prevent this accident occurring occasionally.

Still another means that has assumed importance in some countries is by the agency of the unsterilized communal **hypodermic syringe** of the drug addict (Most, 1940).

In **conclusion** it will be seen that the factors influencing malaria incidence are numerous and complex, and do not allow of facile generalizations. The barest outlines have been given here, and it is for the student of malariology to fill in the details from the extensive literature on the subject, and from personal experience, as there are still many hiatuses in our knowledge.

It will be necessary for the reader to turn again to these pages when the subject of prevention of malaria is discussed.

An exercise.—Meanwhile, by way of an exercise, it might be worth considering an historical epidemiological observation and attempting to explain it in terms of the factors discussed above.

It was observed that whenever a large engineering scheme was attempted in a malarious country, malaria in epidemic form appeared, and frequently the scheme had to be abandoned.

This was explained as the hand of God, a sort of modern version of the tower of Babel, for the gods of all creeds are looked upon as reactionaries by their devotees, or, by the more scientifically minded, as due to 'breaking of the ground' and allowing the escape of poisonous emanations.

What are the causes? Naturally they will vary according to the circumstances, but we will consider the factors common to many such undertakings.

Labour has to be recruited, and this will often come from many parts of the country. Some labourers may come from non-malarious parts and they will be non-immunes; some will come from district A and others from district B, and each will bring with them the malaria strains of their own district against which they themselves enjoy some immunity; and there will also be the locally recruited labourers with their own malaria strains and their own immunity. We placed the malariogenic factors in four main groups; let us consider each.

A. The malaria parasite.—This was already present and conditions were favourable to it, but in our hypothetical case two sets of new strains have been introduced.

B. The mosquito.—Mosquito vectors were already present and the climatic conditions were favourable for them, but engineers have in the past been the mosquitoes' best friends; they deflect streams, they interfere with the natural drainage and periodic flooding, they dig holes in the

ground which fill with water, and in many other ways increase the opportunity for mosquito breeding. In this respect our predecessors were right when they said that 'breaking the ground' caused malaria.

C. Man.—Whereas before in the locality there was one group of people largely immune to the local strains of malaria, there are now (a) the non-immunes, highly susceptible to all strains of malaria; (b) people from district A, largely immune to their own strains but susceptible to the malaria strains introduced from district B and to the local strains; (c) people from district B, susceptible to strains from district A, and to the local strains; and (d) the local labour, susceptible to the new strains introduced from districts A and B.

In addition to this, most of the men are living under unfavourable conditions regarding food, cooking, etc., they are away from their natural surroundings, and are probably very miserable; under these conditions, any immunity that they possessed is probably reduced to a minimum.

D. Links between man and mosquito.—The sites of camps are usually ill-chosen and often placed in the closest proximity to the engineers' worst malarial crimes; the quarters are unsuitable for protection against mosquitoes, and mosquito nets are not provided, nor are the men usually educated enough to use them if they were.

Conclusion.—With such a concatenation of malarial factors, it is easy to see how malaria achieves epidemic proportions.

There will of course be additional factors in some circumstances, and in others all those enumerated above will not operate.

PATHOLOGY

Historical.—Meehl in 1847 pointed out the diagnostic significance of the presence of pigment in the organs; this diagnostic point still holds good, for in no other disease has hæmozoin pigment been found. In the following year, Virchow described the pigment in the peripheral blood, especially in the large mononuclears.

Hæmozoin pigment, which was at one time thought to be melanin, is formed by the malaria parasite from hæmoglobin; it is soluble in ammonium sulphide and has practically all the chemical and physical properties of hæmatin (Sinton and Ghosh, 1934).

The general reaction.—The pathological changes are brought about mainly by the excessive intravascular destruction of red blood corpuscles and the presence of parasitic pigment and debris, and probably to some extent by a toxic substance that is present in the malaria parasite or is produced from the parasitic debris.

The reticulo-endothelial cells in all parts of the body take up this pigment and the red-cell and parasitic debris; as a result of this there is stimulation and proliferation of the reticulo-endothelial tissue, with increased vascularization of the organs affected, and eventually fibrotic changes occur. In the more acute cases, blocking of the arterioles leads to local necrosis and petechial hæmorrhages. The parenchyma cells of the liver and kidney, as a result of overwork in disposing of the products of increased catabolism, undergo degenerative changes. Finally, there are the effects of the problematical malarial toxin; for example, necrotic and degenerative changes have been described in the supra-renal cortex in severe cases of malaria.

The spleen.—This organ being the main site of the reticulo-endothelial tissue in the body shows the most characteristic changes.

The reaction of the spleen in the individual is a subject about which there is no unanimity of opinion. Some workers consider that the degree

of enlargement is a good indication of the extent of the parasitic infection, whereas others claim that the reverse is usually the case. The writer takes the view that splenic enlargement is evidence of imperfect host-parasite adjustment. In hyper-endemic areas, immunity in the child is low, parasitic infections are heavy and considerable splenic enlargement is the rule. In the well-nourished adult, immunity is high, parasitic infections though common are light, and the spleen is small. Finally, in the ill-nourished adult of the poorer malarious districts, immunity is again low, and parasitic infection is kept down only by the continuous parasite—and incidentally red-cell—destruction of the hypertrophied reticulo-endothelial tissues, so that splenic enlargement and anæmia characterize the clinical picture.

Macroscopically. in very acute cases, the spleen is moderately enlarged, dark red and congested; the capsule which is under pressure retracts when it is cut and a dark red substance oozes out. In less acute cases, it is moderately enlarged, firm and slate-coloured; when cut, the capsule does not contract in the same way, but a certain amount of black tarry substance can be scraped away from the slate-coloured cut surface. In chronic cases, the organ is markedly enlarged, the capsule is thickened and shows evidence of past peri-splenitis; the organ may weigh anything up to 10 pounds, but it is firm, not very dark, and shows white fibrous trabeculæ.

Microscopically, there is a general hyperplasia in which both lymphoid and reticulo-endothelial elements take part; later, there is an increase of the reticulo-endothelial tissue at the expense of the malpighian corpuscles. In an acute case these cells are loaded with red-cell and parasite debris and hæmozoin pigment, but, in chronic malaria, parasites may be absent and pigment very scanty.

Other organs.—The liver is enlarged, the gall-bladder is distended, and on section the liver may show a dark red surface, but in certain cases in which there has been very excessive hæmolysis (*e.g.* blackwater fever) there will be a distinct yellowish colour, the result of hæmosiderin staining, in addition to the dark brown of the specific hæmozoin pigment. The organ gives a marked prussian-blue reaction with potassium ferrocyanide. Under the microscope the Küpffer's cells are seen loaded with pigment and debris and the bile canaliculi are dilated; in more chronic cases there are degenerative changes in the parenchyma cells.

The active **bone-marrow** is dark red, but the hyperplasia is mainly confined to the phagocytic reticulo-endothelial cells, which contain pigment and debris, to the detriment of the specialized hæmopoietic tissue. Parasites are usually present in fair numbers, but, from biopsy experience, there is no reason to believe that there is any particular aggregation of parasites in this site.

In fatal malignant tertian infections with cerebral symptoms, there is congestion of the meningeal vessels, and petechial hæmorrhages in the brain. In microscopic sections, the arterioles will be seen to be blocked, and occasionally there are areas where the neuroglia cells have proliferated, forming a granulomatous area around an arteriole, usually in the cortex. The blocking of the arterioles may be caused by sporulating forms, by large sexual parasites, or by aggregations of parasites, but is more frequently due to the ingestion of parasites by, and the subsequent swelling and proliferation of, the endothelial lining cells of the arterioles. This blocking of the arterioles is seen best in a smear made by crushing a small piece of brain cortex between two slides and staining them by Giemsa's method.

The **kidneys** are congested in acute cases, but do not as a rule show any characteristic changes; there are however cases of acute and sub-acute nephritis of undoubted malarial origin, and the rarity of this complication suggests that it may be an allergic phenomenon due to sensitization by the foreign proteins, from parasite and tissue destruction in a previous attack. The kidney changes in this sub-acute attack are of the glomerulo-tubular nephrotic type. In blackwater fever (*q.v.*) there are characteristic changes.

There may be blocking of the arterioles in other organs and tissues of the body, *e.g.* the pancreas and intestinal mucosa; these cause the protean localized manifestations of malaria, such as malarial dysentery and a condition simulating acute pancreatitis.

The degenerative changes attributed to the malarial 'toxin' that occur in many organs are too indefinite to discuss in detail; it is very often doubtful if the changes noted are really due to the malaria or to some concomitant condition.

The blood.—There is nearly always some anæmia; the degree will depend on the duration of the attack and on other circumstances, but it is disproportionate to the number of the red cells that have actually been destroyed by malaria parasites, and in the acute infection there is evidence of depression of hæmopoietic function of the bone-marrow. There is additional indirect evidence for this; the deduction is made from the fact that before treatment is given, though there is anæmia there is at first no rise in the percentage of reticulocytes, but that about six to eight days after specific treatment has been instituted there is a sharp rise in reticulocytes (evidence of sudden active regeneration of red cells), suggesting that some depressing influence has been lifted. These studies have been made mostly in Great Britain and in primary induced malaria; we have not been able to confirm them in malaria in an endemic area. On the other hand, we have found that the bilirubinæmia is very frequently not as high as one would have expected had the anæmia been solely the result of red-cell destruction, that is to say, had it been a hæmolytic anæmia.

The anæmia is usually normocytic.

There is a slight fall in leucocytes which starts just before the clinical attack; the leucopenia is maintained throughout the attack, and sometimes for some days after the temperature has returned to normal; there are usually about 5,000 leucocytes per c.mm. (*see figure 11*). The deficiency is mainly in the granulocytes, and there is usually an actual, as well as a relative, increase in large mononuclears. In the absence of kala-azar and certain rarer blood diseases, a large mononuclear count of 15 per cent or over is said to be diagnostic of present or past malaria.

The van den Bergh indirect reaction may be slightly increased during an acute attack, but it is not constantly so.

The blood sugar is reduced.

The erythrocyte sedimentation rate is much increased whilst the infection persists.

(The specific findings, malaria parasites, pigment, and Schüffner's and Maurer's dots are discussed under the heading of diagnosis.)

Days before and after first appearance of parasites.

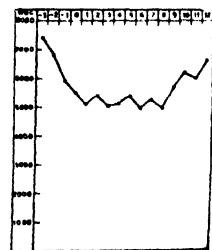


Figure 11 : Mean leucocyte counts for ten patients with *falciparum* malaria. (Kitchen, S. F., 1941.)

The urine.—During the febrile attack, the urine is usually concentrated and exhibits the ordinary 'febrile' characteristics.

Urea excretion is increased and the chlorides and phosphates are often diminished.

Urobilin is increased considerably during the attack. There is quite frequently a trace of albumin at the onset, and in some cases of both quartan and malignant tertian malaria—traditionally in the former, but in the writer's experience just as frequently in the latter—a heavy cloud of albumin and granular and hyaline casts.

Quinine albuminuria was not uncommon when large doses of quinine were the rule, but, with a maximum of 30 grains a day, this seldom occurs.

Wassermann reaction.—Positive Wassermann and Kahn reactions are undoubtedly given in malaria, irrespective of syphilitic infection. Kitchen, Webb and Kupper (1939) found that one or other test was positive in all, and both tests in 23, of 25 induced malarias. From his experience with naturally acquired malaria, the writer is convinced that this so-called 'false-positive' Wassermann reaction frequently occurs in this disease; it is usually transitory but may persist for some weeks. It is however certainly not as constant a finding as the experience with induced malaria, quoted above, would suggest.

SYMPTOMATOLOGY

Historical.—Hippocrates described quotidian, tertian, and quartan malaria, and, from the times that temperatures were first charted, temperature charts of these three types of malarial fever have appeared in textbook after textbook, so that the student is very liable to get an entirely wrong impression of the constancy of these classical types.

Incubation period.—The first symptoms do not appear until the malaria infection has reached a certain critical level; this is usually given as about 100 million parasites.

The variations in the incubation period in different species are explained by simple arithmetic. Let us take the cases of malignant tertian and quartan, and suppose that one sporozoite entered the human host and was allowed to multiply uninterruptedly (both unlikely suppositions but they will serve our purpose); in malignant tertian an average rosette contains 24 merozoites, so that the parasites are multiplied by 24 every 48 hours and the 100 million mark will be passed in 12 days, whereas in quartan, with an average of 10 merozoites per rosette which matures every 72 hours, it would take 24 days to reach the critical figure of 100 million parasites. Many merozoites of course fail to reach a red cell and are destroyed, and there are other factors which put a brake on reproduction, but it is easy to see why malignant tertian with its maximum production of 32 merozoites may have a very short incubation period and why quartan with its low merozoite production and 72-hour cycle is likely to have the longest.

The incubation period of benign tertian is usually about 14 days, in malignant tertian it may be as short as eight days and is usually less than 12, and in quartan it is 20 days or more. Recent work with malaria therapy has shown that the incubation period in the initial attack may be prolonged considerably, but the long-delayed onset after 30 to 40 weeks which has frequently been observed must be looked upon as a late relapse after an inapparent 'attack'.

Prodromal symptoms before the actual onset are not uncommon, lassitude, anorexia, headache and a slight sense of chilliness; if the

temperature were taken, a low pyrexia, 99°F. or so, would probably be found. In cases under close observation, a daily, or a 48 hourly, rise up to 99°F. is the rule; these small rises in temperature correspond with the bursting of successive crops of rosettes before the infection has quite reached the true clinical threshold.

The true onset is sudden; there are three stages in the attack :—

The rigor.—There is a feeling of extreme coldness; the patient shivers from head to foot, sometimes shaking the whole bed; the teeth chatter; he pulls over himself all the blankets he can reach but it makes no difference to his feeling of coldness; the skin feels dry and the condition known as goose-flesh is common; the features become pinched and he has the blue appearance of a cold person. All this time the temperature is rising and after about an hour the shivering gradually ceases and the patient passes into the next stage.

The hot stage.—There is now a feeling of intense heat and the patient will throw off his blankets; the skin is very hot and dry, the face is flushed, the pulse full and bounding, and respirations rapid; the temperature at this stage will be found to be anything up to 106°F., or even higher. He complains of severe headache, a parched throat and extreme thirst; vomiting is common. This stage usually lasts one to four hours, but it may be prolonged.

The sweating stage.—The patient suddenly bursts into a profuse perspiration; the sweat pours from him. A feeling of great relief comes over the patient and all the symptoms of the previous stage disappear. The temperature falls and may be sub-normal. He now feels 'washed out' and tired and will usually go to sleep. When he wakes up he feels perfectly well and is often prepared to get up and go about his ordinary daily routine.

The whole attack occupies six to ten hours. The rigor coincides with the bursting of the rosettes. When a rosette bursts, there is a sudden release into the blood stream of not only the merozoites but of red-cell debris and probably certain products of malaria parasite metabolism. The rigor is an anaphylactic phenomenon, sensitivity having been worked up by the bursting of the earlier crops of rosettes. Manson-Bahr states that the attack usually occurs in the morning, but this is not the experience of the writer; it may occur at any time.

The periodicity of the malarial attack.—This is dependent on the plasmodial cycle, so that in tertian malaria it will occur every 48 hours and quartan every 72 hours, in the ordinary way, but not infrequently two crops of parasites will be completing their cycle 'out of step', that is to say, in tertian malaria, the rosettes of one crop will burst on the even days of the month and the other crop on the odd days, so that the patient will have a rigor daily (Hippocrates' quotidian malaria), or, if the infection is quartan, on two days out of three.

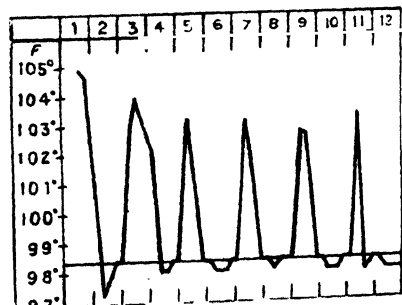


Figure 12 : Benign tertian malaria.

In the initial attack of benign tertian malaria in a non-immune the onset may be with a typical rigor, but much more frequently there is a daily

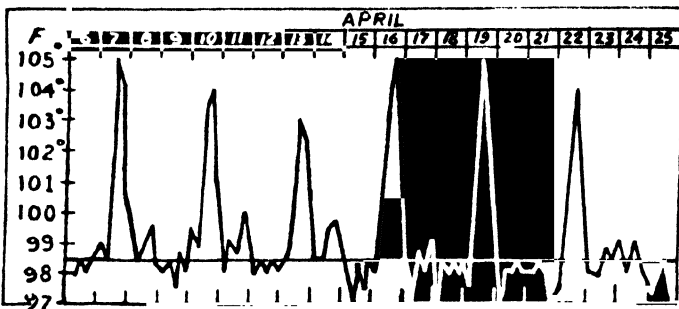


Figure 13 : Double quartan infection with one 'brood' predominating.

rise of temperature for a few days, with or without rigor, then a typical rigor occurs, and subsequently the classical periodicity is observed. In relapses and subsequent attacks the onset will usually be classical.

At the other end of the story, in an endemic area, in-

dividuals with a considerable degree of immunity against the local strains will frequently not show the classical febrile response; the fever may be low and irregular, or even absent, but the parasite may still be doing considerable damage, for example, causing anæmia.

Even in the partly immune individual living in an endemic area, quotidian periodicity is more common than tertian, but not infrequently one crop of parasites dies out, leaving the other crop to continue its 48-hour cycle.

In benign tertian infection **spontaneous remission** is the rule (figure 14), but it may be postponed for a considerable time. Lowe (1934), in a

series of sixteen untreated cases of pure benign tertian infection in partially immune Indians in an endemic area, noted spontaneous remission in eleven cases within fourteen days; in the remaining five, though the infection showed signs of dying out, he gave quinine to save the patients from the debilitating effects of long-continued fever; of the untreated cases three relapsed, but after a few days' fever again recovered spontaneously.

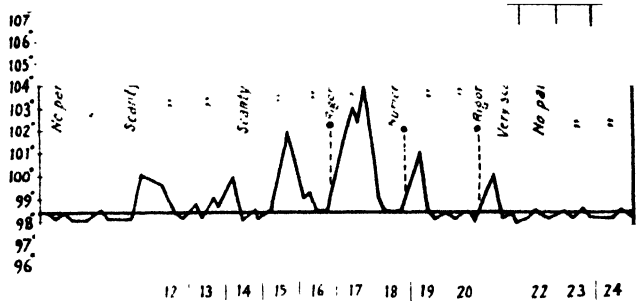


Figure 14 : Induced benign tertian infection with natural subsidence in a partially immune patient (orig.).

Weeks after recovery from primary attack

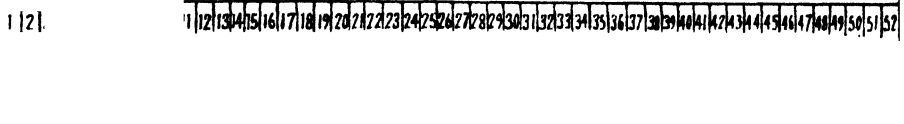


Figure 15 : Time of relapse in 100 cases of relapsing benign tertian malaria (144 relapses).
(James, Nicol and Shute, 1936.)

Benign tertian malaria shows a far greater tendency to relapse after treatment than malignant tertian. Figure 15 shows the times when relapses usually occur. In benign tertian malaria, the late relapse, the peak of which occurs at about the 28th week, probably accounts for the spring rise in malarial incidence that has been reported in some countries where the temperature precludes transmission at this time of year.

Other specific clinical characteristics.—It is by no means always possible to distinguish between the four different malaria infections clinically, except where quartan periodicity is clear, but the different infections have their special characteristics.

In malignant tertian, the temperature chart much less frequently follows the classical form. It is usually remittent and not intermittent, and quite often the temperature is maintained at a high level for 36 hours, only falling a few hours before the next rise; a dicrotic notch in the chart is very common (figures 16 and 17). All the symptoms are more likely to be severe, particularly the vomiting; cerebral symptoms may develop early

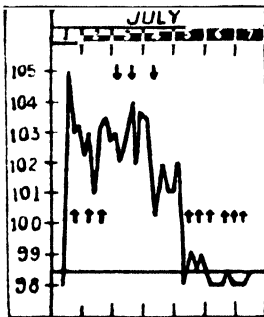


Figure 16 : Malignant tertian malaria showing sustained rise despite treatment

failed to control fever; this necessitated three intravenous injections.

↑ = oral quinine.
↓ = intravenous quinine.

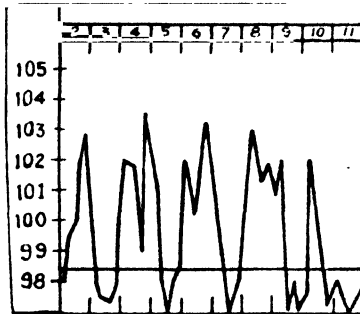


Figure 17 : Malignant tertian malaria showing tertian periodicity.

and, though spontaneous remissions obviously do occur (or the mortality would be much higher than it is), the danger of cerebral symptoms supervening precludes experiments in patients under observation to ascertain how soon remission will occur. Relapses after adequate treatment are not common but when they do occur

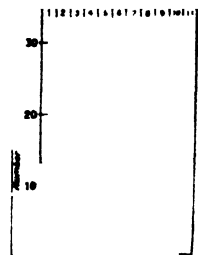
are likely to be as serious as the initial attack.

Figure 18 shows that, if a relapse is going to occur, it will usually occur within the first few weeks.

Quartan malaria is usually no more severe than benign tertian, splenic enlargement is less marked, but nephritis is said to be much more common; in some places it has been reported in 40 per cent of the cases, the albumin in the urine showing an increase with each attack.

Malaria due to *Plasmodium ovale* is very mild, shows a marked tendency to early spontaneous remission, and responds rapidly to treatment.

In an endemic area where more than one species of parasite occurs, mixed infections are very common. In Calcutta, where many cases of malaria are seen, it sometimes takes us many weeks to find what appears to be a pure benign tertian infection; even then, though many films have been searched and only benign tertian parasite found, this blood injected into another man, for purposes of malaria therapy,



relapse of 63 cases of malignant tertian.

will often give rise to a mixed infection, with the dangerous malignant tertian predominating.

Other signs and symptoms of the ordinary attack.—The spleen enlarges during an attack and subsides between attacks, but this frequent enlargement leads to hypertrophy and it tends to become larger at each successive attack. The spleen may not be palpable during the first few febrile attacks of a primary infection, but in re-infections or relapses it provides a valuable indication of the nature of the fever. The spleen has been known to rupture spontaneously during a malarial attack; there is a sudden severe pain in the abdomen, but this is quite often not in the splenic area (*see also* Diagnosis).

The right heart is often dilated during an attack and congestion of the liver may follow. Tenderness of the liver is a very frequent symptom; this is a fact that should be recognized to avoid confusion with amœbic hepatitis.

A feeling of pressure in the thighs and legs, and sometimes actual pain in the legs are symptoms well recognized by patients subjected to frequent malarial attacks.

There is sometimes diarrhœa as a result of the pleocholia, followed by constipation associated with the hepatic congestion. An icteric tinge of the skin and sclerotics, short of actual jaundice, is usual in severe malignant tertian infection. Sweat rashes will be troublesome if the patient is not properly nursed; herpes labialis is common, and urticaria by no means rare.

Acute nephritis may result from either a malignant tertian or a quartan infection. Also a sub-acute glomerular nephritis is a common complication; this condition responds rapidly to quinine (*see figure 19*).

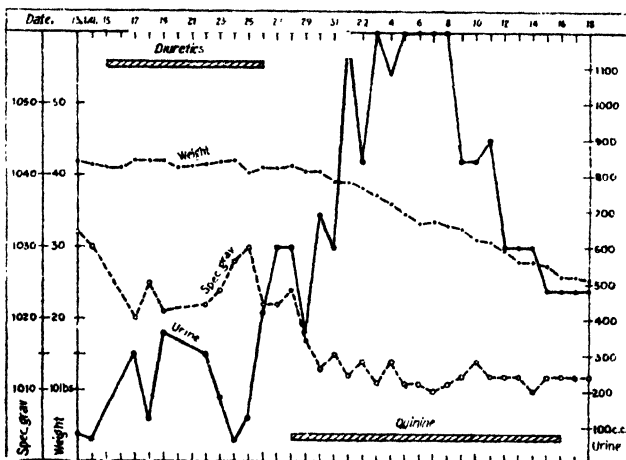


Figure 19 showing the response to quinine in a case of post-malarial glomerular nephritis.

In infants the temperature will seldom run the usual course; it is nearly always a high remittent or even continuous fever, but shows great irregularity. Vomiting occurs early and is frequent. The spleen enlarges rapidly and usually the liver also. Convulsions replace the rigor that occurs in an adult. Very prompt vigorous treatment is necessary, as early death

due to hyperpyrexia and cerebral involvement is common, but a comatose child will often come round completely in a few hours.

In pregnant women, malaria if left untreated will be fatal to the child and dangerous to the woman. Still-birth and abortion are very common; these are sometimes said to be due to the blocking of the placental vessels with subsequent separation of the placenta. This is not the mechanism, since the parasites do not normally reach the placental circulation. The

parasites seem to have a particular affinity for the decidual blood vessels; a blood smear taken from the surface of the placenta after parturition will show a large number of parasites in a case in which few were to be found in the woman's peripheral blood. The decidual vessels are, however, too large to allow blocking by malaria parasites, and the abortion is more likely to be the result of some toxic effect. Malarial subjects are more liable to the toxæmias and to the severe macrocytic anæmia of pregnancy. It is imperative therefore that treatment should be undertaken immediately malaria is diagnosed in a pregnant woman.

SPECIAL CLINICAL TYPES OF MALARIA

A. Pernicious.—This is usually associated with malignant tertian infection, but sometimes with quartan and even benign tertian. The different forms that pernicious malaria may take are almost unlimited, but those most frequently encountered can be grouped as follows :—

(i) **Cerebral forms.**—(a) The heat centre may be affected, the temperature will run up to 110°F., or higher, and death will be inevitable; (b) the onset of the attack may be with coma and delirium without a typical rigor, or after a typical onset this condition may develop rapidly; (c) there may be epileptiform seizures due to involvement of the cortex, or other localizing symptoms, such as aphasia; or (d) there may be psychic manifestations—mania, delusional insanity, or melancholia (such symptoms are sometimes wrongly attributed to the treatment), which may precede the febrile symptoms.

The other symptoms associated with the cerebral type are a full bounding and rapid pulse, a flushed face, sighing respirations, and vomiting.

In these cases the differential diagnosis from heat stroke, apoplexy, epilepsy, diabetic coma, meningitis, alcoholism, and trauma may be difficult.

(ii) **Algid forms.**—There may be sudden collapse with no other symptoms or this collapse may be associated with hæmorrhagic vomiting, with severe choleraic diarrhœa, muscular cramps and suppression of urine, with dysenteric symptoms—blood and mucus in the stools, or with other localizing abdominal symptoms suggesting, for example, hæmorrhagic pancreatitis.

The characteristic symptoms in the algid form are collapse, a weak thready pulse, sometimes barely perceptible, a cold clammy skin, a weak voice, and slow shallow respirations. The patient may recover fairly rapidly or may pass on into a 'typhoid state' for some days. The localizing symptoms are due to the blocking of the arterioles by malaria parasites in the particular locality, as occurs in the brain in the cerebral forms.

(iii) **Bilious remittent fever.**—This is a form of severe malignant tertian malaria that was distinguished clinically from the ordinary malarial attack in the days before the parasite was discovered. It seems less common in these days, possibly because it is recognized as a malarial manifestation and treated earlier. The attack starts as an ordinary malignant tertian fever, but it is associated with very severe nausea and vomiting, and jaundice appears on the second day of the fever; this will increase for a few days and then subside with the attack. It is distinguished from the jaundice of yellow fever or Weil's disease by its early appearance and its tendency to disappear, whereas in the other conditions jaundice does not appear until later and, in yellow fever in particular, it increases steadily.

(iv) **Blackwater fever.**—[This will be considered separately.]

(v) Other types that do not fall into any of the above groups are the **cardiac** and the **broncho-pneumonic**. They are self-explanatory.

B. Chronic malaria.—This term is falling into disfavour with the malariologist, probably rightly so, because its exact meaning is not clearly defined. There is, first, the **chronic relapsing malaria** that is usually simply malaria that has been inadequately treated. Even after a full course of cinchona, the relapse rate in benign tertian is high and the treatment may have to be repeated for two, three, or even more relapses, but eventually it will respond. It is surprising how many people there are, including doctors, who after a single infection will allow themselves to suffer for years for want of adequate treatment.

In the next group are those persons who are subjected to **repeated infections** for years, often throughout their lives which are not necessarily short. This group should really be sub-divided into those that are infected periodically, for example, where malaria is definitely seasonal, and those that are infected perennially. This subject has not been sufficiently studied and the different reactions of the individual to these repeated infections satisfactorily explained. In some, the parasites will be found in the peripheral blood whenever it is examined, but the hosts seem to suffer very little disability, though they may have slightly enlarged spleens, which are residual from their childhood reactions to malaria infection, and they may be slightly anæmic (though not on clinical observation). There are others who suffer periodic attacks of fever, are weak, debilitated, and anæmic, have enlarged spleens, are very subject to other infections, and are altogether of poor value to the community; on proper treatment, these patients will recover completely and again become really useful members of society.

Finally, there is the **chronic malarial cachexia**. The patient has a huge spleen and liver, œdema and often ascites, he is very anæmic, has an earthy complexion and often some jaundice, he may or may not have low fever but in any case he is usually too ill and miserable to take much notice of this, and he is very subject to bowel and lung infections which eventually end his miserable life. There is a tendency to dismiss this condition as not being due to malaria but to other infections, such as kala-azar or bilharziasis, but this sequel, as perhaps it should be called, to malaria is undoubtedly very common in many endemic areas, though parasites are not often present and the patient does not respond well to anti-malaria treatment.

What determines the different reactions to malaria infection in different classes and in different individuals is not definitely known, but in the writer's opinion diet is a very important factor; the meat-eating African tribes show parasites in the peripheral blood, but, once immunity is established in childhood, suffer very little from the infection, whereas the Bengal ryot on a very poor diet with a low protein and vitamin content shows all the different stages of chronic malarial morbidity up to the stage of malarial cachexia.

C. Latent malaria.—This is an interesting and sometimes important phenomenon of malaria infection. It may be commoner than we imagine, but it can only be demonstrated properly in a person who leaves the place where he has been infected and lives in a malaria-free country. It is not uncommon in people returning home from the tropics when they are subjected to the rigours of an English winter; other physical strains, such

as surgical and obstetric operations, will often bring out a latent infection in any individual who has no knowledge of a previous attack. In such cases the parasites are so scanty, and are possibly hiding in the tissues of some internal organ, that a previous blood examination would not reveal their presence were a blood examination made, and it is therefore advisable to give a course of cinchona as a routine measure before the confinement of, or a surgical operation on, anyone coming from a highly malarious area.

DIAGNOSIS

The diagnosis should be considered under five headings—the history, the fever, the spleen, the blood film, and response to therapy.

A. The history.—Before making a diagnosis of malaria one should be satisfied that the patient, at some time, even if not recently, has been in a malarious country. Latent malaria will seldom, if ever, make its first appearance more than a year after infection; the last possible chance that the patient had of being infected should be carefully ascertained. Other possibilities of infection, from a blood transfusion and from an unsterilized hypodermic needle, *e.g.* the communal needle of the drug addict, should not be forgotten. On the other hand, it is dangerous to assume that just because a person has been in the tropics, he is certain to be ‘riddled with malaria’; there are many who, like the writer, have lived for 25 years in the tropics without having a single attack of malaria.

A history of a previous attack is also suggestive, but here again it is necessary to be cautious, because to the layman in the tropics fever is synonymous with malaria and the patient should be questioned as to whether a diagnosis was made on a blood examination, whether the typical rigor and malarial periodicity were exhibited, and whether there was response to cinchona (or mepacrine). Undue weight should not be given to the answer to the last question.

B. The fever.—The classical fever charts of tertian and quartan malaria are pathognomonic, but one does not, except under very rare circumstances, see such a chart, for, if the patient is intelligent enough to take his temperature, he is usually intelligent enough to make his own diagnosis and institute treatment; however, a clear history of rigors on alternate days or every 72 hours is often obtainable from the less sophisticated patient and is very helpful. The writer has seen colourable imitations of malarial periodicity in non-malarial subjects, but this periodicity is only accidental and is not usually maintained for any length of time.

On the other hand, malaria must not be excluded just because the temperature chart does not conform to any of the classical types and rigors are absent; the chart may take almost any form in uncomplicated malaria, and malaria may be complicating any other disease.

C. The spleen.—There are many other diseases in the tropics that are accompanied by splenic enlargement. It is more important to know if the spleen is enlarging than to observe that it is enlarged. Rapid enlargement, and the increase and recession during the febrile attack and intermission, respectively, are the most suggestive features. The spleen is slightly tender and firm; this is to be compared to the very soft spleen of typhoid. In chronic malaria, as the spleen enlarges it becomes firmer, and eventually assumes a wood-like hardness, as a result of the fibrotic changes that have taken place; in these stages it is not tender.

In tropical practice, unless the spleen is palpable with the patient lying on his back with his legs drawn up, or standing and bending forward slightly,

the enlargement is not usually of much importance; the apparently painful contortions sometimes depicted in textbooks are not to be recommended.

D. The blood film.—The examination of the blood film is the most important procedure in the diagnosis of malaria.

Even one or two doses of cinchona or other anti-malarial drug will make the finding of parasites very difficult, so that the blood should be taken (but not necessarily examined) before any such drug is given.

Whilst one would not recommend postponing the taking of the blood film, it should be remembered that immediately after a rigor, though the parasites will be most numerous, the large majority will be very young, and therefore very small, rings; these are not as easy to find as the larger trophozoites of some hours later. (It is on this principle that the so-called 'malaria culture' method is useful; *in vivo* there is some mortality amongst these developing parasites and they also disappear into the internal organs, but *in vitro* they develop unhampered and become more conspicuous, though no actual multiplication takes place.)

Methods of examining the peripheral blood.—The blood can be examined by the thin film, the thick film, and the so-called cultural methods. The last-named is a refinement that is worth undertaking when any special investigation is being carried out and where facilities exist, but a negative 'culture' cannot be accepted as conclusive evidence of the absence of parasites. It is not a method that one would recommend as a routine procedure, and it need not be described here.

The Romanowsky-stained thin film is the method most frequently used, but the thick-film method is gaining popularity as the technique of this method improves. The value of the thick-film method is that a much larger quantity of blood is examined and a scanty infection, especially of gametocytes, can be recognized. The disadvantages are that the number of parasites cannot be estimated so accurately; that the parasites themselves may be distorted and their relationship to the red cells cannot be observed, so that though they are recognizable as malaria parasites their species may remain uncertain; and that any special features of the red cell such as size, stippling, Schüffner's and Maurer's dots, etc., are not seen so readily. For these reasons, both a thick and a thin film should be made.

For purposes of diagnosis the thin film should be examined first, and if parasites are seen the thick film may be discarded; but if they are not found within a few minutes the thick film can be stained and examined; when parasites are found in the latter and their identity is uncertain, a return to the thin film can be made and this re-examined with more confidence. It is much easier to find parasites when you know they are there, than when you just think they may be there.

For malaria survey work, it is usual to examine the thick film for the presence of malaria parasites, and subsequently the thin film if their identity is required; in these circumstances, both thick and thin films are often made on the same slide. In this type of work, it may be important to estimate the exact number of parasites; this is easily and accurately done by mixing with the blood an equal quantity of fowl's blood-corpuscle suspension of known concentration.

A thin blood film is then made from the mixture; this is stained, and field by field the number of fowl's red corpuscles (easily distinguished by their oval shape and nuclei) on the one hand and malaria parasites on the other are counted.

The ratio of one to the other is worked out and, as the number of fowl corpuscles per c.mm. is already known, the number of malaria parasites can be calculated.

Finally, the giving of **adrenaline** to cause a contraction of the spleen, so that parasitized red cells in the spleen sinuses are forced into the circulation, is a method worth employing in hospital cases, when parasites cannot be found by any of the above methods. Either 0.5 c.cm. of 1 in 1,000 adrenaline should be given subcutaneously, 20 minutes before, or 0.01 c.cm. intravenously, five minutes before, the blood is taken; the latter will be more effective.

Technique.—The first essential in making a good thin film is to have perfectly clean slides and a good spreader. The coverslip of a hæmocytometer makes an almost ideal spreader. Otherwise, one should select a good thick microscopic slide with a good edge and cut off the two corners* to make the spreading edge slightly narrower than the slide on which the film is to be spread.

The blood can be taken from the lobe of the ear or the finger. The part should be previously sterilized with alcohol and ether, but it must be allowed to dry completely, or be rubbed with dry sterile cotton-wool. The needle, which should be a sharp bayonet-pointed or triangular surgical needle, must be similarly sterilized and dried. A sharp deep prick is made, and when the drop of blood appears the surface of the slide is applied, so that it just touches the drop but not the skin of the finger or ear. The drop should be taken on the slide about a quarter of an inch from the end. The slide is then placed on a flat surface with the drop upwards, the spreader is applied to the centre of this slide, and is slid towards the drop until it touches it, when the blood will spread along the edge of the spreader; this can be assisted by a little lateral movement. When the blood has spread completely along the edge of the spreader, the latter is held at an angle of about 30° with the slide and is pushed along towards the centre of the slide. The blood follows the spreader leaving an even film on the slide, until it is exhausted when film begins to form 'tails'. The size of the drop of blood should be such that 'tails' begin to form about, or just beyond, the centre of the slide (figure 20).

Staining blood films.—All blood smears should be stained within 24 hours. If the smears cannot be stained immediately, they must be fixed with methyl alcohol and stored in a dust-proof slide box for staining at a later date. The unstained slides must never be left uncovered on the working table as blood is readily eaten by flies during the day and by cockroaches at night.

Romanowsky stains, especially those as modified by Leishman, Wright, Jenner, and Giemsa, are the most satisfactory. All these stains depend for their action on the compounds formed by the interaction of methylene blue and eosin, and the differences between the various stains are dependent on the proportion of the two dyes. The fluid stains, except Giemsa's stain, are prepared by dissolving the dry powder in acetone-free pure methyl alcohol, so that a preliminary fixation with methyl alcohol is only required in the case of Giemsa's stain. Leishman's and Wright's stains are used in the strength of 0.15 per cent, and Jenner's stain in the strength of 0.5 per cent.

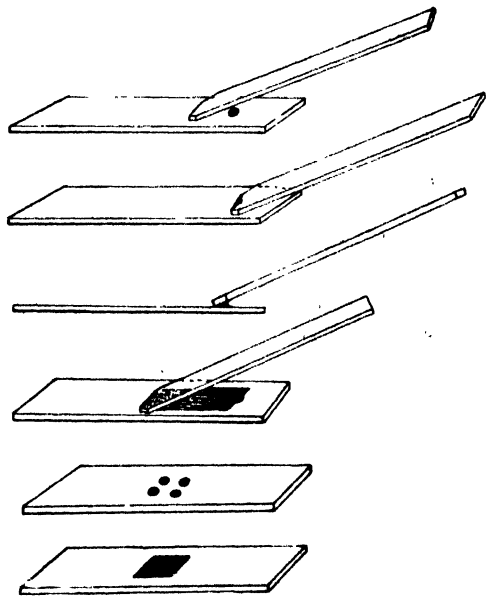


Figure 20 : Methods of making thin and thick films.

* This can be done by making a scratch across each corner with a glass cutter, or very simply by holding the slides under water in a basin and cutting off the corners with an ordinary pair of scissors.

Preparing Leishman's stain.—Stains in powder or tablet forms and extra-pure acetone-free methyl alcohol for dissolving them should be obtained from some reliable firm. We have found the Gurr's* stains to be very satisfactory.

All the glassware used in preparing the stains and in storing them should be scrupulously clean, and free from any trace of water; they should be rinsed first with absolute alcohol and finally with a little methyl alcohol.

Take a weighed amount—say, 0.15 gramme—of stain in powder or tablet form in a small glass mortar. Measure out the requisite amount of methyl alcohol—100 c.cm.—in a graduated glass cylinder. Pour out about 2 c.cm. of methyl alcohol on the stain and grind well to make it into a thin paste. Add in small quantities at a time about half the total amount of methyl alcohol, grinding all the time. Carefully decant the supernatant dissolved stain into a clean glass-stoppered bottle. Add more methyl alcohol to the undissolved stain, grinding as before. Again decant the supernatant stain into the bottle, and continue the process until all the methyl alcohol is used up. If this is properly done all the stain will go into solution and no residue will be left. Place the bottle with the stain in the incubator at 37°C. for 24 hours, after which it will be ready for use.

Staining with Leishman's stain.—Put the slides on a staining rack taking care that the side with the blood film is upwards; also see that the two ends of the slides are in the same plane.

From a drop bottle, or with a pipette, pour on sufficient stain to cover the whole of the film; wait for one minute to allow for proper fixing; with a capillary pipette now add two to three parts of distilled water (pH 6.8 to 7.0) or the buffer solution†. With a capillary pipette or glass rod, thoroughly mix the stain with the diluent to ensure of uniform mixture over the film.

When the mixture is allowed to settle, a scum will form on the top, if the proportion of the stain and diluent is correct. Allow the diluted stain to act for 5 to 10 minutes.

The diluted or undiluted stains on the slides must not be allowed to dry up at any stage of the staining. Drying is prevented by covering the staining rack with a wide bell-jar, or other improvised device; this is a very necessary precaution in hot dry climates.

When the staining is complete, hold one end of the slide firmly with a pair of forceps, and place the stain-flooded slide under a running tap. This will wash off all the stain from the upper surface, while the bottom is cleaned by rubbing it well with the fingers of the left hand. The slide is now transferred to the beaker containing fresh distilled water and gently shaken to and fro until the colour of the smears becomes faintly pink. Now take it out of the beaker, wash it again under the tap and allow it to dry. In order to dry it without allowing dust to adhere to the stained surface, the slide should be sloped against a vertical surface, *e.g.* a wall or the side of a box, with the film side inwards.

When it is dry the slide is ready to be examined.

Staining with Giemsa's stain.—It is more difficult to prepare this stain and it is better to purchase it in solution. Giemsa's stain as prepared by Gurr is very satisfactory.

For staining with Giemsa's stain, preliminary fixing with methyl alcohol or some other fixative is absolutely necessary.

Preparing dilute solution.—Take about 20 c.cm. of prepared distilled water (pH 7.0) or buffer solution in a clean transparent glass cylinder, add 20 drops of undiluted stain, or in other words as many drops of stain as there are cubic centimetres of water. Mix well by inverting the cylinder and see that the depth of colour of the mixture is such that, when held in front of the eyes, it allows a distant object to be seen through it.

* George T. Gurr, 136, New Kings Road, London, S.W.6, England.

† Monopotassium phosphate—6.63 gm.

Anhydrous disodium hydrogen phosphate—2.56 gm. (or 6.46 gm. of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$).

Distilled water up to 1 litre.

Add 1 c.cm. of chloroform as preservative.

Place the slides to be stained on a staining rack, flood the slide with methyl alcohol and cover with a bell-jar, so that the methyl alcohol does not dry up on the slide. Allow the methyl alcohol to act for about three minutes, remove the jar and thoroughly wash with distilled water.

Now flood the slide with the diluted stain, cover with a bell-jar and allow the stain to act for at least half an hour, or better still leave it overnight. Next morning wash and dry the slide as suggested above.

The thick film.—This is made by taking on to the middle of a slide four drops of blood arranged at the corners of an area about half an inch or one centimetre square, and then with a needle or the edge of another slide joining up these drops and spreading them evenly over the square area. The thickness of the film should be such that the blood on the surface is just mobile when the slide is tilted. Trial and error alone will teach one the exact thickness that should be aimed at, but it is better to err on the side of making the film too thin (*see* figure 20, p. 85).

Staining.—Two methods of staining the thick film are described. The former is the method that has been in use for many years at the Calcutta School of Tropical Medicine and provides a result suitable for detailed morphological studies, whereas the latter (Field, 1941) is a simpler and quicker method more suitable for practical use.

Method I.—The film should be allowed to dry for two hours at room temperature or in a bacteriological incubator (37°C.) for one hour.

Dehæmoglobinize the film with the following solution :—

2.5 per cent solution glacial acetic acid	..	4 parts
2.0 per cent solution crystalline tartaric acid	..	1 part

This mixture keeps indefinitely; it should be kept in a glass-stoppered bottle.

Lay the film on the staining rack and gently flood it with the mixture. This process should be watched, as thick patches will take longer than the rest to dehæmoglobinize; complete dehæmoglobinization is indicated by the whole film becoming greyish-white.

As soon as dehæmoglobinization is complete, drain off the fluid by gently tilting the slide. Flood the slide with methyl alcohol, and allow this to remain for five minutes. The film is now dehæmoglobinized and fixed.

Drain off the methyl alcohol and wash the film very thoroughly with neutral or very slightly alkaline distilled water. Every trace of acid must be removed.

Stain the film with dilute Giemsa's stain, one drop to each cubic centimetre of distilled water, for 20 minutes or longer. Wash in distilled water. Do not blot the film, but let it dry by slanting it against a vertical surface, film side inwards.

Method II.—For this method two solutions are required :—

Solution A

Methylene blue	0.8 gm.
Azure I	0.5 "
Disodium hydrogen phosphate (anhydrous)	5 "
Potassium dihydrogen phosphate (anhydrous)	6.25 "
Distilled water	500 c.cm.

Solution B

Eosin	1 gm.
Disodium hydrogen phosphate (anhydrous)	5 "
Potassium dihydrogen phosphate (anhydrous)	6.25 "
Distilled water	500 c.cm.

Preparation of solutions.—The phosphate salts are first dissolved, then the stain is added. Solution of the granular azure I is aided by grinding in a mortar with a small quantity of the phosphate solvent. The solutions of the stain should be set aside for two hours when, after filtration, they are ready for use. Should a scum later appear on the surface, or the dye precipitate on the stained films, subsequent filtration is necessary.

The stains are kept in covered jars of such a size that the depth of the solution is about 3 inches, the level being maintained by the addition of fresh stain as necessary. Eosin solution should be discarded if it becomes greenish.

Technique.

- (i) Dip the film for three seconds* in solution A.
 - (ii) Remove from the solution A and immediately rinse by waving *very gently* in clean water for a few seconds until stain ceases to flow from the film and the glass of the slide is free from stain.
 - (iii) Dip for five seconds in solution B.
 - (iv) Rinse by waving *gently* for 2 or 3 seconds in clean water.
 - (v) Place *vertically* against a rack to drain and dry.
- 3.—The American equivalent of the German azure I is azure B.†

Identification of the parasites.—(See plate II, frontispiece). In the thin film, the parasites, especially the larger forms, will be found mostly at the tail end of the film. They are always within the red corpuscles, though the larger forms occupy practically the whole of the corpuscle and only a shadow-like ring or segment of a disc represents the remains of the host cell.

The ring is the form of which the largest number appear in the peripheral blood; the young ring form consists of a ring of light-blue cytoplasm with a vacuole in the centre and a dark-red chromatin dot at one point on the periphery. The chromatin may take a rod-like form, or appear as a double dot, and, though it is actually red, in a slightly over-stained film it appears almost black. The ring forms of the different species differ; the smallest and most delicate is that of *P. falciparum* and it is the only form of the asexual cycle that is seen in the peripheral blood in malignant tertian infection; whereas the *P. vivax* trophozoite is seen in all its stages in the peripheral blood and from the beginning develops an irregular amœboid appearance with a large chromatin mass. As the parasite grows, the cytoplasm becomes more amœboid, sprawling all through the corpuscle and eventually almost filling it, pigment appears, the chromatin divides into irregular masses, and the unoccupied portion of the red cell shows fine eosinophil stippling known as Schüffner's dots. *P. malariae* is not so amœboid but the ring is coarser than that of *P. falciparum* and the chromatin globular rather than rod-shaped; the growing trophozoite usually takes the form of a band, with the chromatin in one mass and the pigment scattered, stretching across the red corpuscle which does not ordinarily show any stippling.

The so-called *accolé* form of *P. falciparum* appears as a thin strip of cytoplasm attached to the surface of the cell.

When the trophozoite is fully developed schizogony commences, the chromatin divides, and the parasite becomes a *schizont*; in *P. vivax* the outline is now regular, the parasite is usually oval in shape and occupies about two-thirds to three-quarters of the corpuscle; the chromatin and pigment are scattered throughout the cytoplasm of the parasite; in *P. malariae*, the schizont almost fills the enlarged corpuscle, and the pigment granules are collected into a single mass.

* Field recommended one second in each solution.

† Should azure I or azure B be unobtainable it is possible to prepare a methylene-blue-azure mixture of undefined composition from medicinal methylene blue.

- (i) Dissolve 1.3 gm. of medicinal methylene blue and 5 gm. of anhydrous disodium hydrogen phosphate (Na_2HPO_4) in 50 c.cm. of distilled water.
- (ii) Bring to boil and then evaporate on a water-bath almost to dryness.
- (iii) Add 6.25 gm. of anhydrous potassium dihydrogen phosphate (KH_2PO_4).
- (iv) Add 500 c.cm. of distilled water, stir until the stain is completely dissolved, and set aside for 24 hours.
- (v) Filter before use.

The final stage of schizogony is the **rosette**. The chromatin is divided up into a number of equal portions each of which is associated with a small portion of cytoplasm to form small round nucleated bodies (**merozoites**) which, tightly packed together with hæmozoin pigment in the centre, form the rosette. The number of merozoites in each rosette varies according to the species; for practical purposes, if there are 12 or less, it is probably a quartan parasite (*P. malariae*), if more than 12, it is probably a benign tertian (*P. vivax*). (A *falciparum* rosette is seldom seen in the peripheral blood, and the inexperienced should hesitate to diagnose a rosette as *P. falciparum* unless there are at least 32 merozoites.)

Isolated merozoites are not usually seen in the peripheral blood. The other forms seen in the blood are the **gametocytes**. The most characteristic of these is the crescent of malignant tertian (*P. falciparum*). The crescent is much longer than the diameter of a red corpuscle, so that it appears to extend beyond the red corpuscle, the pale outline of which is to be seen in the concavity of the crescent. The female is a long slender crescent, stains a dark blue, and has a compact nucleus around which the pigment is aggregated. The male gametocyte is stouter and less characteristically crescentic, with a large nucleus, the pigment scattered, and the cytoplasm staining a pale blue.

The gametocytes of *P. vivax* are not so frequently encountered in the peripheral blood; they are round or ovoid and fill the corpuscle; the chromatin is aggregated into one mass; the pigment is scattered; and if there are any visible remains of the red corpuscle Schüffner's dots will be seen. The gametocyte of *P. malariae* is usually much smaller than that of *P. vivax*, but otherwise very similar. As in the case of *P. falciparum*, the nucleus in the female is more compact, and the staining of the cytoplasm darker.

The changes in the containing red corpuscles that occur are characteristic. In benign tertian infection (*P. vivax*), the cell is pale and considerably enlarged, and it exhibits regular fine eosinophil stippling throughout. The red corpuscle that contains the very young ring forms of *P. falciparum* is not enlarged, and in fact may appear to be smaller than normal, but is really more globular. When the trophozoite enlarges, however, the cell also enlarges slightly, becomes slightly darker, and shows numerous Maurer's dots, or clefts; these are red or purplish, coarser, and much more irregular than Schüffner's dots. The red corpuscle in quartan (*P. malariae*) infection is similarly more globular but does not show Maurer's dots.

The **pigment** in benign tertian is a fine and lightish brown, in malignant tertian it is coarser, black, and forms clumps, and in quartan, it appears early, is very prominent, and falls between the other two in the matter of colour and coarseness.

P. ovale has not been included in this description up to the present, as it is a comparatively rare plasmodium. It is very similar to *P. vivax*, except that it is not amœboid and the rosette contains 8 to 12 large merozoites; the red corpuscle which is only slightly enlarged shows more marked stippling than in *P. vivax*, but is of a slightly paler red. The special characteristic of the red cell in this case is the frequency with which it assumes an ovoid shape—it is from this and not from the shape of the parasite that its name is derived—or shows a fimbriated edge. (This fimbriation must occur during spreading and is an indication of some characteristic physical change within the cell rather than of any changes in shape that occur *in vivo*.)

TABLE I
Identification of species of malaria parasites

Parasite	Changes in red cells	Pigment	Trophozoites	Adult schizonts	Merozoites	Gametocytes
BENIGN TERTIAN (<i>Plasmodium vivax</i>). 48-hour cycle.	Large and pale with fine red stippling (Schüffner's dots).	Fine, yellowish-brown granules or rods.	Rings $\frac{1}{2}$ - $\frac{3}{4}$ diameter of red cell; growing forms very irregular, with pale blue staining and indistinct outline. Vacuole present.	Completely fills red cell. Irregular in shape.	Medium size; 14-24 in number.	Round or ovoid, larger than red cell. * With deep-blue-staining cytoplasm and small compact nucleus. † Cytoplasm stains more faintly blue or reddish with larger paler nucleus.
QUARTAN (<i>Plasmodium malariae</i>). 72-hour cycle.	Not enlarged. No stippling.	Coarse, dark brown or almost black. Appears early.	Rings $\frac{1}{2}$ - $\frac{3}{4}$ diameter of red cell; growing forms often band-like or angular. Cytoplasm dense; early pigment.	Fills red cell. Daisy-head rosette.	Large size; 8-10 in number.	Round or ovoid, the size of a red cell. * Stains deep blue with small dark compact nucleus. † Stains pale blue or pink, with a large pale nucleus.
MALIGNANT TERTIAN (<i>Plasmodium falciparum</i>). 48-hour cycle.	Not enlarged, spherical and show coarse stippling (Maurer's dots).	Blacker than in other forms; clumps early.	Young forms are fine, hair-like rings, about $\frac{1}{2}$ diameter of red cell; with 2 chromatin dots and <i>accolé</i> forms common. Larger rings are also seen. Growing forms very rarely seen.	Extremely rare in peripheral blood.	Very small. Number variable, 8-32 or more.	* Crescentic, staining deep blue, with a compact central nucleus with pigment aggregated round it. † Sausage-shaped, staining pale blue, with larger and paler nucleus and scattered pigment.
<i>Plasmodium ovale</i> . 48-hour cycle.	Very slightly enlarged; paler than normal. Stippling like <i>P. vivax</i> but coarser. Ovoid or distorted. fimbriated cells.	Coarser than in <i>P. vivax</i> . Dark yellowish brown.	Rings about $\frac{1}{2}$ diameter of red cell; not amoeboid; cytoplasm dense, well defined; chromatin large; may be irregular.	Mature forms slightly smaller than red cell; daisy-head rosette.	Large size; 8-12 in number; sometimes crescentic.	Like <i>P. malariae</i> ; in stippled red cells.

To summarize, identification of the species depends on (i) changes in the red corpuscles, (ii) the nature of the pigment, (iii) the character of the trophozoites, (iv) the presence of the mature schizont—for they do not appear in the peripheral blood in malignant tertian (*P. falciparum*) infection—and their character, particularly with reference to the number of merozoites in the rosette, and (v) the character of the gametocytes. The data are summarized in table I which is a modification of the table given by Covell (1939).

Significance of the findings.—The finding of a malaria parasite naturally indicates that the patient has a malaria infection, but it does not necessarily mean that all his symptoms are due to malaria, for he may have some other disease and malaria may only be an intercurrent infection, or his immunity may be such that the malaria parasites are not actually giving rise to any symptoms at all. Again, the presence of one species of parasite, even if one is absolutely certain about its identity, does not preclude the presence of other species as well, and only recently the writer had the experience of inoculating blood from a patient who showed not only typical quartan parasites but typical quartan fever periodicity, and yet the recipient developed malignant tertian malaria.

Nevertheless, the presence of parasites cannot be ignored from the point of view of treatment, even if one is certain that they are not the cause of the whole symptom complex.

Conversely, there are many occasions on which one will fail to find parasites in a true case of untreated malaria, as any honest protozoologist will admit. The importance of making a definite protozoological diagnosis cannot be over-emphasized, nor can one condemn too strongly the practitioner who assumes that all fever in a malarious country, or even in a malarial subject, is malaria. Nevertheless, after a very thorough though unsuccessful attempt to make a parasitological diagnosis, it is sheer folly to withhold treatment in a case in which other evidence points to malaria.

In the ordinary malarial attack, parasites are usually present in the peripheral blood and are easy to find. They may however be scanty and it is easy to overlook the fine rings of the malignant tertian parasite in a thin film; a thick film will help in these circumstances. There are local variations to this rule, and in some localities the parasites in an ordinary case are very scanty in the peripheral blood. Other circumstances in which the parasites are often difficult to find are, (i) at the beginning of a primary attack, (ii) in residents in an endemic area who have acquired a degree of immunity to local strains, (iii) in chronic malaria with splenomegaly, and (iv) after a few doses of an anti-malarial drug.

Regarding the identity of the parasites, even an experienced laboratory worker often finds it very difficult to be certain on the evidence of a single parasite, but after examining an average film for five minutes it should be possible to find enough forms to make identity certain. Mixed infections are however very common, and may cause confusion.

The finding of hæmozoin pigment is also pathognomonic of present or past malaria infection. This is found in the large mononuclear and polymorphonuclear leucocytes. This pigment is unmistakable when it has been seen a few times, but the inexperienced are liable to make mistakes in both directions; they may dismiss true pigment as an artefact, for it looks very like foreign matter superimposed on a cell, or they may mistake stain debris and dust for hæmozoin pigment.

The increase in large mononuclears to 15 per cent will be a point of diagnostic value in some countries, but will not differentiate malaria from certain other protozoal diseases, *e.g.* kala-azar, and in any case may only indicate past malaria.

E. Response to therapy.—There is probably no other disease in which the therapeutic test is more frequently and justifiably used. As has been said above, the experienced protozoologist will often fail to find parasites in a case of malaria; when therefore there is any suspicion in the mind of the physician that the fever from which the patient is suffering is malaria, he should prescribe a course of some efficient anti-malarial drug. Though the occasions on which this treatment will be contra-indicated by the possible alternative diagnosis are very few, it should not be given indiscriminately in every case of fever occurring in a malarious country.

If the therapeutic test is decided upon, an adequate course must be prescribed, and, unless a definite diagnosis of some other disease is made in the meantime, the course must be completed. Ten grains of a standardized cinchona alkaloid mixture, or of quinine alone, twice daily for five days, or, if the synthetic preparations are preferred and available, one and a half grains (0.1 gramme) of atevrin, or of some other preparation of *B.P.* mepacrine, three times a day for five days, may be considered an adequate course.

There are few cases of malaria in which the fever will not respond to five days' adequate specific treatment; on the other hand, it must be remembered that there are many short fevers that simulate malaria (in such cases the temperature would have come down without treatment), and also that the cinchona alkaloids have a febrifuge action in some non-malarial febrile conditions. Therefore, though a *negative* diagnosis in a case in which the fever does not respond may be made with considerable certainty, it is very dangerous to make a *positive* diagnosis of malaria on the therapeutic test.

DIFFERENTIAL DIAGNOSIS

The conditions which malaria may simulate are so numerous that a textbook of medicine would have to be written to deal adequately with the subject, and even a complete list of diseases from which malaria has to be distinguished would occupy an unjustifiable amount of space; therefore, only the main headings under which the differential diagnosis of malaria has to be considered, with the most important examples in each case, are given :—

Fevers. *Short.*—Influenza, bronchitis, dengue, sandfly fever, relapsing fever, filariasis, and local inflammations.

Longer.—Tuberculosis, pyelitis, cystitis, malignant endocarditis, kala-azar, enteric, the typhuses, the undulant fevers, Hodgkin's disease, glandular fever, and gynaecological and other chronic inflammations.

Splenic enlargements.—Leucæmia, splenic anæmia, and syphilis, as well as the febrile diseases mentioned above, kala-azar, typhoid, etc.

Anæmia.—Ancylostomiasis, hæmolytic and other anæmias.

Cerebral.—Heat stroke, meningitis, apoplexy, epilepsy, diabetic coma, alcoholism, narcotic poisoning, and trauma.

Abdominal.—Dysentery, cholera, appendicitis, cholecystitis, and liver abscess.

Jaundice.—Weil's disease, yellow fever, infective hepatitis, and catarrhal jaundice.

Cardiac. pulmonary and nephritic conditions.

TREATMENT

Historical.—Cinchona bark which has been one of the indigenous medicines of South America, probably for millenia, was first introduced into Europe as treatment for malaria, according to tradition* by the Countess of Chinchon, the wife of the Spanish Viceroy of Peru, about the year 1638. The fame of this bark spread rapidly—for those days—through the world and it was apparently introduced into India about twenty years later.

The subsequent history of the drug in India is interesting, for early in the nineteenth century it was almost entirely abandoned in the treatment of malaria. This surprising occurrence is easier to understand if one remembers that the diagnosis of malaria was clinical only and that there are many other fevers that simulate it. A long run of failures to get any response to cinchona therapy, because the disease was not malaria, might conceivably prejudice a physician against the drug. Also as powdered bark only was used and not the extracted alkaloids, it is probable that consignments of bark, which were all imported from South America, varied considerably in their alkaloidal content and therefore in their efficacy. Though for some years there was a semi-official ban on the use of the drug amongst practitioners of 'western' medicine, we cannot believe that a large number did not continue to use this invaluable drug surreptitiously. The treatment that was advocated in its place was heroic purging, with calomel in particular, and, of course, blood-letting. Doses up to 60 grains of calomel were given and it was quite common for a patient to lose all his teeth from the mercurial gingivitis caused by this treatment.

Cinchona bark came back into favour in India towards the end of the first half of the nineteenth century. This return was assisted considerably by the work that had been done on the separation of the different alkaloids by the French chemists, Pelletier and Caventou, in 1820. Plants and seed were brought from South America in 1860 and cinchona cultivation was started in India.

In 1866, the Madras Cinchona Commission was formed to investigate the relative value of the various alkaloids of cinchona bark; they came to the conclusion that quinine was the most useful alkaloid, although the other crystalline alkaloids were also active in the treatment of malaria. This important and scientifically sound observation had very serious repercussions later.

The cultivation of cinchona flourished for some years in India and Ceylon, until in the year 1887 Ceylon alone produced 16 million pounds of cinchona bark. This uncontrolled growth of the cinchona industry led inevitably to the disastrous slump which ended in the ruin of the cinchona plantations, so that by the end of the century cinchona planting as a private enterprise had ceased in India. Java survived this slump and has enjoyed a virtual world monopoly in the cinchona industry ever since.

In 1931 a committee of the League of Nations Health Organization laid down a minimum standard for a cinchona-alkaloids mixture that was efficient and at the same time could be prepared from the harder cinchona plants, without the prior separation of the various alkaloids, or the addition of quinine; this they called 'totaquina'.

After the war of 1914-18, the German chemists stimulated by the fact that they had no colonies in which they could grow cinchona, attempted to find a synthetic substitute for quinine, and in 1926 Professor Schulemann produced the quinoline compound, plasmochin, which, important though it is, has only a limited application in malaria therapy. This was followed a few years later by an acridine compound which was given the name 'atebrin'. The writer had the privilege of being the first physician not connected with the manufacturers to give a clinical trial to this drug and with his colleagues at the School of Tropical Medicine published the two first papers on the subject to appear in any medical journal (Napier and Das Gupta, 1932; Napier, Butcher and Das Gupta, 1932).

*The Countess of Chinchon tradition has now been exploded (Haggis, 1932). The Countess about whom the picturesque story is told never went to Peru, and her successor, who did, never had malaria, never used the 'miraculous bark', and never returned to Europe. The true story appears to be that cinchona bark first reached Europe from South America as a fraudulent adulterant of another bark, which was reputed to have anti-febrile properties and was called quina-quina locally. The superior qualities of the adulterant were eventually recognized, but it still retained the name under which it was originally foisted on European consumers.

Cinchona requirements.—The world quinine requirements have been placed at 1,387,412 kilogrammes annually (League of Nations, 1932). In India, it has been conservatively estimated that to treat her one hundred million sufferers from malaria at least a million pounds of cinchona alkaloids are required. About 70,000 lbs. of cinchona alkaloids, of which quinine forms the bulk, are produced in India annually; the average amount consumed is 200,000 lbs. which leaves a balance of 130,000 lbs. to be imported. Nearly nine-tenths of the world's quinine supplies come from Java. Cultivation in the Philippines has been developing during the last few years. There is now little cultivation in South America, the natural home of cinchona. No other country produces cinchona in any significant amounts.

The cinchona alkaloids.—Cinchona bark contains four crystalline and a number of amorphous alkaloids. The four former, quinine, cinchonine, quinidine and cinchonidine, all have anti-malarial properties. Of the individual alkaloids, quinine is undoubtedly the most valuable, as it is the most powerful and produces the least adverse by-effects. Of the other alkaloids, cinchonidine, which like quinine is laevorotatory, is the most useful, being no more toxic and almost as effective as quinine; cinchonine if given in too large doses is liable to irritate the gastro-intestinal tract; and quinidine is well known for its depressing action on the heart and is used in medicine extensively for this purpose. A preparation of the crystalline alkaloids mixed in the proportions in which they occur in many samples of bark forms an anti-malarial drug which is very nearly, say 95 per cent, as effective as the pure quinine salt and which in only 2 or 3 per cent of patients will produce any adverse symptoms. The amorphous alkaloids have a poor anti-malarial action and tend to make the tablets—a convenient form in which the mixed cinchona alkaloids are often given—hard and insoluble.

Quinine salts.—Quinine base being very insoluble, the drug is usually given in the form of one of its salts. The most generally useful is the sulphate, though it is not very soluble in water and has to be prescribed with acid in the mixture. The bihydrochloride is the most soluble, but, making a very acid solution, it causes pain when given intramuscularly, and therefore the neutral hydrochloride salt is preferable for this purpose.

The dihydrobromide is conveniently soluble, but contains a smaller amount of the alkaloid and therefore 25 per cent should be added to the dose when this is prescribed in the place of the sulphate, and more when it replaces the bihydrochloride. It is reported to give rise to less cinchonism, but possibly this is accounted for by its lower alkaloidal content.

The ethyl carbonate is insoluble in saliva and therefore tasteless, but it dissolves in the normal gastric juice. It is not however fully absorbed and it is generally stated that 8 grains of the ethyl carbonate of quinine (euquinine) correspond to 5 grains of the sulphate.

The strength, solubility, and reaction of the commoner salts of quinine are as follows :—

Salts.	Percentage of quinine base.	Solubility in H ₂ O at 25°C.	Reaction.
Sulphate ..	74	1 in 720	Neutral.
Hydrochloride ..	82	1 in 18	"
Bisulphate ..	59	1 in 8	Strongly acid.
Bihydrochloride ..	82	1 in 0.75	"
Dihydrobromide ..	60	1 in 6	Neutral.
Ethyl carbonate ..	82	nil	Alkaline.

Cinchona plants.—There are many different species of cinchona; these vary considerably in their alkaloidal yield. *Cinchona ledgeriana* gives the highest yield of crystalline alkaloids and particularly of quinine, but it is a comparatively delicate plant and will only grow well at certain altitudes and within certain restricted ranges of temperature and humidity. *C. succirubra* was the first species planted in India; it has a comparatively poor alkaloidal yield and so low a quinine yield that for this purpose it is totally uneconomical to grow, but it is a very hardy plant and will grow over a much wider range than *C. ledgeriana*.

There are other plants, e.g. the hybrids, *C. officinalis* and *C. robusta*, that, whilst they have a comparatively high alkaloid yield though short of that of *C. ledgeriana*, are very much hardier than *C. ledgeriana*, and will grow over a much wider range of climatic conditions.

Totaquina standard.—The standard laid down for totaquina (introduced into the B.P. 1933) is that it shall contain at least 70 per cent of crystalline alkaloids, of which 15 per cent must be quinine; the amorphous alkaloids must be less than 20 per cent, mineral matter less than 5 per cent, and moisture less than 5 per cent. The cinchona febrifuge grown in the government plantations and prepared in the government factories in Bengal complies, for all practical purposes, with this standard. A recent analysis of a sample showed that it contained 32 per cent quinine, cinchonine 11 per cent, quinidine 1 per cent, cinchonidine 30 per cent, and amorphous alkaloids 15 per cent.

Cinchona policy.—One of the main reasons that Java gained and has kept this world monopoly was that they have large areas of country that are particularly suited to the growth of the high-quinine-yielding varieties of cinchona plant, e.g. *Cinchona ledgeriana*, and the world demand has during the last 50 years been almost entirely for quinine and not for the other alkaloids that might also be used in the treatment of malaria. It is natural that, if only one of the four available alkaloids is used and the others are more or less wasted, the price of the one alkaloid will have to be greater than if all four were saleable, for the planter must make his living. This has led to the price of quinine being comparatively high, and the high price of quinine is an important adverse factor in malaria control in rural areas.

A committee of the League of Nations Health Organization studied this question of the high price of quinine. They decided that, although no country could hope to produce quinine in competition with Java, many could grow other cinchona plants that would produce a comparatively high yield of total alkaloids from which a preparation of mixed alkaloids of cinchona could be produced at a very much lower price than that of quinine. Another advantage would be that by growing these other cinchona plants on a large scale many poor countries could provide their own cinchona requirements and become independent of imported quinine. The committee realized that one of the reasons for the unpopularity of the preparations of mixed cinchona alkaloids was that there was no standard for 'cinchona febrifuge', as such mixtures were usually labelled, so that any waste product from the manufacture of quinine could be labelled cinchona febrifuge and sold as a malaria specific. Many of these mixtures had some anti-malarial action, but this was so far below that of quinine and they so frequently produced gastro-intestinal and other unfavourable symptoms, that they naturally fell into disrepute.

The unfortunate impression has arisen that cinchona febrifuge is a cheap and inferior substitute for quinine which is foisted on poor people who cannot afford quinine. This was of course true of some but not of all cinchona febrifuges, and the international totaquina standard has given us a means of distinguishing between the good and the bad preparations. Only such preparations that are stated to be of 'totaquina standard' should be used.

The next step taken by this committee was the organization of experiments to show the relative efficacy of totaquina as compared with quinine. These experiments have shown that totaquina is very nearly if not quite as efficacious as quinine in the treatment of malaria. The writer's experience has been that it is perhaps even more efficacious in benign tertian infections.

India was only one of the countries which the committee of the League of Nations Health Organizations had in mind, but in no country could their work have more important repercussions if the government would take advantage of

the situation. Though India is not so fortunate as Java in her climate, *vis-à-vis* the cultivation of the high-quinine-yielding *C. ledgeriana*, she has nevertheless vast areas in which the hardier, *C. robusta* and *C. officinalis*, would grow, and if the government would either undertake, or control and guarantee to protect, large-scale cinchona planting, an efficient anti-malarial drug at one-quarter the present price of quinine could be produced, and further India would become entirely independent of imported quinine*.

The synthetic anti-malarials.—There is a very great future in this line of chemical research. The initial successes that have been achieved are very encouraging, and we believe that when chemists and pharmacologists can again turn their full attention to this subject more efficient and less toxic compounds will be found.

The first of the successful anti-malarial drugs to be synthesized was plasmochin (*B.P.* pamaquinum); this is N-diethyl-amino-isopentyl-8-amino-6-methoxy-quinoline. Originally introduced for the treatment of the malarial attack and the destruction of the asexual forms, plasmochin has now been found to be too toxic, in the doses in which it has to be given, for this purpose. It is however the only drug that has any appreciable direct action on the gametocytes, particularly those of malignant tertian. Also it enhances the action of quinine and mepacrine in completely eradicating a benign tertian infection and thereby preventing a relapse. In these two capacities, it acts in very small doses, far below the toxic level.

Cilional, di-alkylamino-alkylamino-oxy-quinoline, a drug closely allied to plasmochin but much less toxic, has an action similar to that of plasmochin; it has however to be given in much larger doses to produce the same effect.

Another successful preparation is atebtrin (*B.P.* mepacrinæ hydrochloridum), or dihydrochloride of 2-methoxy-6-chloro-9- α -diethylamino- δ -alkylamino-acridine. This drug is less toxic; in normally non-toxic doses it destroys the asexual forms of the four species of plasmodium and controls the malarial attack, but it does not act on the gametocytes of *P. falciparum* and has little and doubtful action on those of *P. vivax* and *P. malariae*; it is therefore similar in action to quinine.

There are now a number of preparations that are apparently identical with atebtrin, *e.g.* crinodora, quinaerine, and recently British and American firms have also placed on the market preparations that are chemically identical with plasmochin, *e.g.* præquine.

Mechanism of action of anti-malarial drugs.—Our knowledge on this subject is not really very clear yet; it is believed that the cinchona alkaloids act indirectly by stimulation of the natural defences of the body, and do not have a direct action on the parasites, for *in vitro* they survive in a dilution of 1 in 10,000 which is a much higher concentration than ever occurs in the blood. The first result of quinine administration is not to reduce their numbers or to have any adverse action on the trophozoites or schizonts, as these are seen to be numerous and apparently unaffected

* The writer, as Editor of the *Indian Medical Gazette*, has for the last eleven years repeatedly urged the government to adopt a policy of extended cinchona growing and alkaloid distribution. Early in 1942 the Japanese invaded Java, and India's external source of cinchona vanished. It has been possible to increase India's internal production to about 80,000 lbs. a year which is about 8 per cent of the real requirements and 40 per cent of her average annual consumption for some years. Recriminations are useless, but the writer feels that he may be allowed just this one 'I told you so'. The writer is informed that Mysore, Travancore and Ceylon are already starting cinchona plantations, and cultivation in the Government of India plantations in Sikkim, Bengal and Madras is now being extended.

shortly after quinine administration. It is suggested that the action may be on the merozoites whilst they are free in the blood, either directly or by altering the charge on the red cells so that the merozoites are not attracted to, or are unable to enter, the red cells. The clinical evidence that the action of quinine is greater during the sporulating stage is inconclusive; the action on the sexual forms of *P. vivax* and *P. malariae* is poor and on those of *P. falciparum* is nil.

On the other hand, the action of atebirin is a direct one; the molecule is attached firmly to the parasite which shows obvious signs of degeneration very shortly after the drug is given.

Absorption and excretion.—By whatever route the cinchona alkaloids are given, the eventual fate of the drug is much the same.

Given by mouth to a normal individual quinine is absorbed very rapidly, and appears in the blood within about 15 minutes and in the urine within about half an hour; it reaches its maximum concentration in the urine in 5 to 9 hours, and is practically all excreted within 24 hours.

Given intravenously, 95 per cent of the quinine is removed from the blood almost immediately; it is then reabsorbed, and subsequently it behaves in very much the same manner as quinine given by mouth, except that a high concentration in the blood is reached slightly earlier.

Given intramuscularly, it usually appears in the blood and urine almost as quickly as when given intravenously, but occasionally it is held up in the muscles, for some reason probably connected with the blood supply of the part of the muscle into which it is injected.

PRINCIPLES AND AIMS OF SPECIFIC TREATMENT

It will be advisable first to analyse our aims in the treatment of malaria, and we must consider treatment in the widest sense, that is, treatment to prevent as well as cure the disease. The objects that we may hope to achieve by specific drug treatment can be placed under five headings :—

(1) *True causal prophylaxis*; the destruction of the sporozoites injected by the mosquito before they enter the red cell and commence their intra-corporeal cycle.

(2) *Clinical prophylaxis*; the administration of a drug that will prevent the infected person from suffering from an attack of clinical malaria, but without necessarily destroying all the parasites in that patient*.

(3) *The treatment of the clinical attack.*

(4) *Treatment to prevent relapses.*

(5) *Gametocyte destruction in the cause of general prophylaxis.*

(1) **True causal prophylaxis**; that is to say, the destruction of the sporozoites injected by the mosquito before they enter the red cell and commence their intra-corporeal cycle.

There is at present no drug which will achieve this. Ten grains of quinine given daily for five days before and nine days after a person has been infected by a mosquito will not prevent the development of the parasite, nor will atebirin in full therapeutic doses followed by a daily dose of 0.1 gramme.

In an experiment carried out in London, in which some half-dozen well-known malaria workers took part, three daily doses of 0.02 gramme of

* For this, the army favours the expression 'suppressive treatment'. There are points in favour of this term, provided that it is not used in a disparaging sense, as it often is. The writer prefers the better established 'clinical prophylaxis'.

plasmochin (a dose which will sometimes produce toxic symptoms) were given for one day before and six days after the infective mosquito bite, and yet five out of six of these men became infected.

The discovery of a drug that will act on the sporozoites would mark a great advance in malaria therapy.

(2) **Clinical prophylaxis**; that is to say, the administration of a drug that will prevent the infected person from suffering from an attack of clinical malaria, but without necessarily destroying all parasites in that patient.

Now this *can* be done. A dose of 0.2 gramme (three grains of atebrin given twice a week, or a daily dose of six grains (five grains are sometimes insufficient) of quinine will usually keep a person free from clinical malaria, even in a very malarious place, for an almost indefinite period.

Field experiments.—A large-scale experiment has recently been carried out in Malaya in an estate labour force. In one group everyone was given atebrin on two consecutive days during the week—adults had a dose of 0.2 gramme each day and children correspondingly smaller doses, as shown in the table below. In another group six grains of quinine were given daily to adults, and children were given smaller amounts, as shown in the table.

Ages, years	Atebrin, grammes	Quinine
1 to 2	.. 0.025	or 0.1 g. euquinine* (1½ grains).
3 to 4	.. 0.05	or 0.2 g. euquinine (3 grains).
5 to 6	.. 0.075	} or 0.2 g. quinine bihydrochloride.
7 to 8	.. 0.1	
9 to 10	.. 0.125	
11 to 12	.. 0.15	or 0.4 g. quinine bihydrochloride.
13 to 16	.. 0.175	

A third, control group received no specific treatment. The results of this prophylactic treatment are shown in figures 20 and 21 (Field, Niven and Hodgkin, 1937).

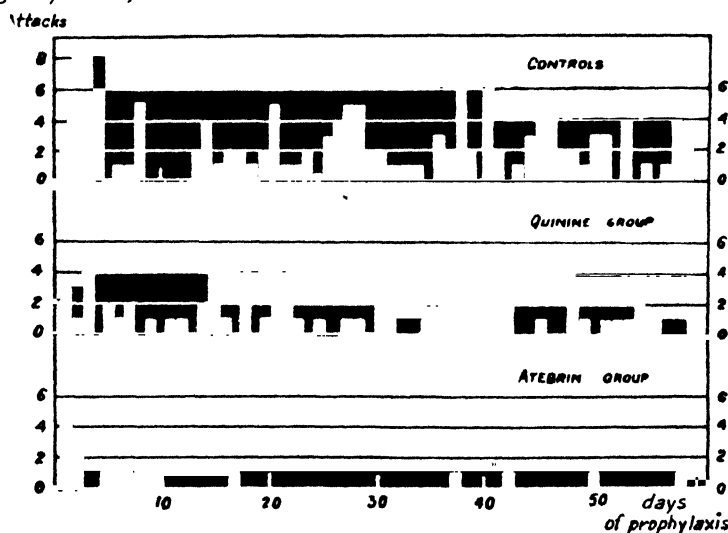


Figure 20 : Immediate effect of prophylactic measures.

It will be seen that in the atebrin series the malaria was controlled almost immediately and only an occasional case occurred : in the quinine

* Euquinine or quinine ethyl carbonate is insoluble in the mouth and therefore tasteless, whilst it contains 82 per cent of the alkaloid, actually more than quinine sulphate (74 per cent), its lower solubility in the gastro-intestinal tract makes it advisable to give it in the relatively larger doses indicated.

series the control of the malaria was slower but eventually it was largely effected.

The important point however is that even in the atebtrin group, they were only kept free from fever *as long as the atebtrin dosage was continued*; this dosage did not produce *true causal prophylaxis* and did not eradicate the malaria infection completely, but kept it at a sub-clinical level, so that when the drug was discontinued a very large number of the patients suffered a clinical attack of malaria almost immediately and nearly 80 per cent within two months.

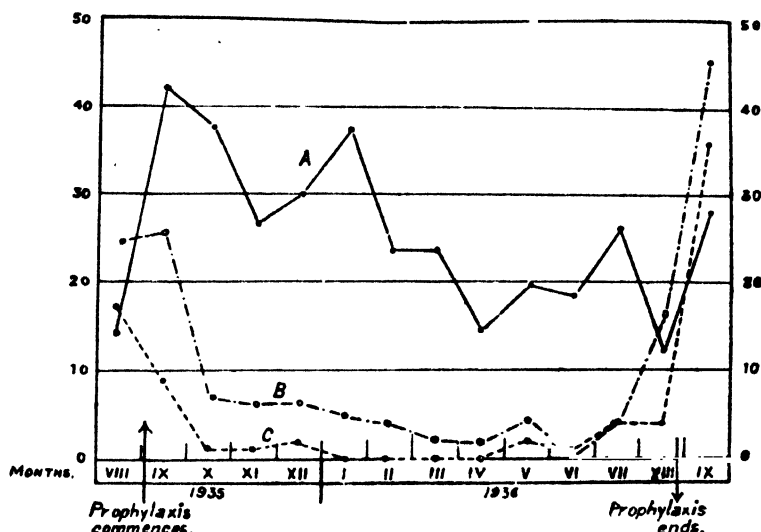


Figure 21 : Monthly incidence of malarial attacks.

Number of subjects.

A = Controls	91 ± 14
B = Quinine 0.4 gramme daily.	91 ± 17
C = Atebtrin 0.4 gramme weekly.	103 ± 12

This is shown in figure 21 which gives the malaria incidence month by month for more than a year. It will be seen that, when in the control group there were nearly forty cases monthly, in the atebtrin group there were none, or only one or two. However, directly the prophylactic treatment was withdrawn, the incidence in the atebtrin group rose to 37 and was actually higher than in the control group. Lamprell (1940) in a similar experiment in Assam obtained an exactly comparable result.

These field experiments suggest that the administration of these drugs, whilst keeping the infection below the clinical level, interferes with the full development of immunity, so that when the drug is withdrawn not only do latent suppressed infections become apparent but immunity to fresh infections is much less developed than in the patients of the control series, in whom the infections were allowed to run their natural course and immunity was allowed to develop.

It is thus apparent that drug prophylaxis in a labour force should only be carried out in special circumstances, either as a stop-gap whilst other anti-malarial methods are being organized, or as a temporary measure to keep the largest possible number of workers in the field during a particularly busy time of year; this second reason will apply to armies operating in

malarious countries, and the adoption of this measure might well determine the success of a campaign.

Individual drug prophylaxis.—The question naturally arises, should one advise the individual in a malarious district to take anti-malarial drugs as a prophylactic measure? A clear-cut answer cannot be given as the circumstances are subject to such wide variations. Where a European, or other foreigner, is touring in a malarious tropical country, in such circumstances that he (or she) is likely to be bitten by a malaria-carrying mosquito, he should certainly take a prophylactic drug, and atebryn is in this case probably the drug of choice; it should be taken in prophylactic doses (p. 98) during the whole stay in the malarious country and for a week after leaving it, after which a full therapeutic course should be taken (p. 101).

(It should however be mentioned that though drug prophylaxis is most useful in the case of the casual visitor, it will actually be less effective in a non-immune individual than in one who has acquired some immunity through previous experience of malaria.)

If this same person is residing for perhaps some years in a slightly malarious country he should not depend on drug prophylaxis, but take all other prophylactic measures (*vide infra*) to avoid infection; at the same time, if he is still running some risk of infection, drug prophylaxis should be used as an extra precaution, but in these circumstances, in view of our lack of knowledge of the effects of atebryn over a very long period, the writer would advocate quinine (six grains daily) again throughout the whole period of risk and for a short time afterwards.

As the daily dose of quinine is not without its unpleasant and possibly mildly detrimental effects, it cannot be advocated lightly and in circumstances where the individual is not exposed to great risk of malarial infection, either because the area is one of moderate malarial endemicity or because he is adequately protected by other measures. However, no definite rule can be laid down, and local custom should be taken into account, though not followed blindly, for local conditions may have undergone a change as a result of other anti-malarial measures, and old-established foreign residents in tropical countries are liable to be unreasonably conservative.

There is no reason to suppose that prophylactic quinine is ever seriously detrimental, or that it increases the risk of blackwater fever occurring in a subject who takes it, as has been suggested; it is not the regular taking of quinine that is the predisposing factor in this serious sequel of malaria, but the frequent omissions to take it.

For the indigenous inhabitant or the permanent settler in a malarious country, it is very questionable if drug prophylaxis should ever be attempted; it is better by letting the subjects suffer periodical attacks, which can be treated before serious symptoms appear, to allow them to work up their immunity, and to devote the money available to the general improvement of their economic condition, and to other preventive measures.

(3) **Treatment of the clinical attack.**—In the very great majority of cases, the clinical attack can be terminated easily and rapidly by the administration of atebryn*, quinine, or standardized cinchona febrifuge (*B.P. totaquina* standard) given by mouth. Plasmochin* has no place in treatment under this heading.

* The writer has used the words 'atebryn' and 'plasmochin' in preference to the official 'mepacrine' and 'pamaquine', as the former are at present more familiar, but the references are not necessarily to the proprietary preparations with these names.

Before discussing specific treatment, mention must be made of a recommendation of the Health Committee of the League of Nations, which has been severely criticized, but with which the writer is in part agreement. They recommend that in the *initial* attack of malaria the patient should be allowed to remain untreated for a few paroxysms in order that he may work up his natural immunity before he is given any anti-malarial drug.

This suggestion is based on reliable experimental evidence and it is no doubt absolutely sound advice, in theory, but in practice it is seldom possible to do this, as in most cases the patient's only desire is to be cured of the immediate attack, and if one insisted he would simply call in another doctor. It is, in any case, only advocated in benign tertian infection.

If cinchona or quinine are given the prescriptions should be :—

R Totaquinæ (or cinchona febrifuge) ..	g. x	or R Quininæ sulphatis ..	g. x
Acidi sulphurici dil. ..	min. xx	Acidi citratis ..	g. xx
Magnesi sulphatis ..	g. xxx	Aquam chlorformi ad	℥i
Aquam chlorformi ad ..	℥i		

One or other of these should be given twice daily in benign tertian infection and three times daily in malignant tertian infections and this dosage should be continued for seven days.

If atebirin is used 0.1 gramme (or $1\frac{1}{2}$ grains) should be given three times a day for five days—or in severe malignant tertian infections this may be continued for seven days, but not longer.

For women and small or weak men, this dosage may be too high, and it may be advisable to reduce the 10 grains of quinine to $7\frac{1}{2}$ grains; in each case the adult dose of atebirin is usually well tolerated.

Children both need and are able to take relatively larger doses of quinine than adults: the dose in grains is calculated as 1 to $1\frac{1}{2}$ *plus* half the age of the child in years (*e.g.* give a well-nourished child of five years of age $1\frac{1}{2} + \frac{5}{2} = 4$ grains). This is best given, twice or thrice daily according to the species of the infecting plasmodium, in treacle or honey, preferably in the form of the tasteless (euquinine), but if this salt is given the dosage must be increased by 50 per cent.

The *total* daily dosage of atebirin for children should be :

1 to 2 years	0.05 gramme ($\frac{3}{4}$ grain)	9 to 12 years	0.2 gramme (3 grains)
3 to 4 "	0.075 " ($1\frac{1}{4}$ ")	13 to 16 "	0.25 " (4 ")
5 to 8 "	0.1 " ($1\frac{1}{2}$ ")	Over 16 "	0.30 " ($4\frac{1}{2}$ ")

The total dose is divided into two or three individual doses, as is most convenient.

In the very great majority of instances oral administrations will be sufficient and effective. The reason for this is that when the drug is given by the mouth to a healthy person it is absorbed by the gastric mucosa immediately, and within about half an hour it will have appeared in the urine. By whatever route it is given, it will not reach the systemic blood circulation faster than this. There are, however, some cases in which there is no response to oral administration and the various reasons for this are given below.

Possible reasons for failure of oral administration.—(i) Absence, or a shortage, of quinine in the so-called quinine mixture. This may be due to the dishonesty or carelessness of the dispenser or of the manufacturer; many instances have been reported in which serious consequences have resulted.

(ii) Faulty preparation of the tablets, that is, they may be insoluble through the presence of too much amorphous alkaloids, or because they are coated with some insoluble substance.

(iii) Vomiting of the mixture or tablet.

(iv) Failure of absorption by the gastric mucosa.

(v) Deception by the patient himself, or herself, on account of prejudice (pregnant woman) or malingering.

The methods that can be recommended to circumvent some of these occurrences are to test the stock mixtures by means of the simple method originally suggested by Megaw, and to test the urine of the patient by the Tanret-Mayer test for the presence of quinine, or for atabrin by the method of Tropp and Weiss (1933).

Test for quinine in mixtures.—The reagent is made up as follows:—Pure phosphotungstic acid—1 ounce, dilute sulphuric acid—5 ounces, and rectified spirit—12 ounces. Place 2.5 c.cm. of the reagent into each of two narrow tubes; add to one 0.25 c.cm. of the quinine solution to be tested and to the other 0.25 c.cm. of a control mixture containing the amount of quinine that the mixture was supposed to contain, *e.g.* 10 grains to the ounce. A precipitate forms which will settle and the two tubes can be compared in half an hour's time. Any gross deficiency will be obvious.

Tanret-Mayer test for quinine in urine.—The reagent is made as follows:—Add a solution of 1.45 grammes of mercuric chloride in 80 c.cm. of undistilled water to a solution of 5 grammes of potassium iodide in 20 c.cm. of distilled water, agitating the solution all the time. To test the urine, first boil and then filter it, then add a few drops of reagent to 5 c.cm. of the urine: an immediate precipitate forms if the alkaloid, quinine, is being excreted in the urine.

Test for atabrin in the urine.—Add 2.5 c.cm. of 60 per cent NaOH and 25 c.cm. of ether to 50 c.cm. of urine; shake well, allow the ether to separate, pipette it off, and to it add 5 c.cm. of N/10 hydrochloric acid. The intensity of the yellow colour will be in proportion to the atabrin content of the urine.

The question of administration of anti-malarial drugs by routes other than *via* the mouth can now be discussed.

Parenteral therapy.—There are two routes by which anti-malarial drugs can be given parenterally (*παρά* = besides; *εντερον* = intestine), namely, the intramuscular and the intravenous; we will consider them together first.

The points for and against these methods of administration may be considered under the following headings:—

(i) *Necessity.*—In certain circumstances parenteral therapy is essential, as for example in unconscious patients and in cases where there is persistent vomiting.

(ii) *Advantages.*—The main advantages are that one gives the injection oneself and is therefore certain that it has been taken, and further that it has been absorbed. Quicker action is claimed by some workers, but this is at the best very slight.

(iii) *Dangers.*—These are not very great *provided* sufficient care is taken. Intramuscular injections require scrupulous asepsis, and great care must be taken to avoid large nerves, or neuritis or paralyses may be caused.

In intravenous therapy, the injections must be given *very* slowly and the drug must be well diluted, or syncope and collapse may occur.

(iv) *Abuses.*—To give parenteral injections as a routine measure in the treatment of malaria is unnecessary and therefore a definite abuse.

Even when parenteral therapy is indicated, it is seldom necessary to continue it beyond the first day; after this oral therapy can usually be instituted (see figure 22).

The intramuscular versus the intravenous route.—On the subject of parenteral therapy, there are acute divergences of opinion in the ranks of the medical profession. Extreme views are taken: there is the school of thought mainly amongst private practitioners, which considers that no treatment for malaria is complete without a few intramuscular injections, and the opposite school which looks upon an intramuscular injection of quinine as little short of malpraxis; this latter has been the 'official' view and for a number of years there has been an 'official' ban on intramuscular injections. Textbooks, teachers, and even regulations have been uncompromising in their condemnation of this method of administering quinine. Research workers have been called in and have supported very strongly the official view; they have shown that the injected quinine causes local necrosis, so that the slightest sepsis will lead to abscess formation and possibly extensive tissue destruction, which may cripple or even kill a debilitated patient. There is also the danger of tetanus. These dangers are all real, though they may be very slight, and the writer has seen both deaths and serious crippling result from intramuscular injections. Nevertheless, there are in the tropics many observant and careful practitioners who do not hesitate to give intramuscular injections of quinine whenever they think that parenteral administration is indicated.

Though the writer does not feel justified in criticizing all practitioners who resort to the intramuscular route much more frequently than he does, he does condemn whole-heartedly the practice of giving quinine by intramuscular injection as a routine procedure.

The writer's own point of view is that only in one in a hundred cases of malaria is the parenteral route indicated, and where it is indicated the intravenous route is preferable ninety-nine times out of a hundred. In the ten thousandth case he would not hesitate to give an intramuscular injection.

Preparations and dosage.—*Intravenous.*—Ten grains of quinine dihydrobromide in 20 c.cm. of normal saline or 5 per cent glucose, repeated about six hours later, or atebirin musonate 0.125 g. (0.1 g. atebirin hydrochloride) in 3 c.cm. of distilled water, given three times in the day. Quinine must be given very slowly, not faster than 2 c.cm. (or 1 grain) per minute by the watch, with or without 0.5 c.cm. of pituitrin.

Intramuscular.—Ten grains of quinine dihydrobromide, or 10 grains of quinine hydrochloride with five grains of urethane* in 2 c.cm. of distilled water; this makes a solution with hydrogen-ion concentration of about pH 6.0 and is preferable to the bihydrochloride which forms a very acid solution (pH 3.5).

This is given into the gluteus maximus, the vastus externus, the muscles at the angle of the scapula, or the deltoid; or atebirin musonate 0.375 g. (0.3 of atebirin hydrochloride) in 9 c.cm. of distilled water, into one of these muscles.

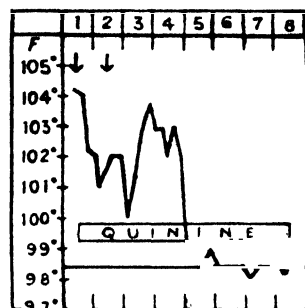


Figure 22: Malignant tertian malaria, heavy infection, with vomiting: two intravenous injections of quinine (indicated by the arrows) and quinine by mouth for seven days.

* Urethane acts as an analgesic and also increases the solubility of the salt.

(4) **Treatment to prevent relapses.**—The big-stick methods which were at one time popular, large daily doses of quinine over long periods, are no longer considered sound practice. The average case of malignant tertian infection will not usually relapse after the ordinary curative dose of cinchona, quinine, or atabrin, but as relapse may be serious a second course after an interval of 7 to 10 days is usually advisable; the same remark applies to quartan infections. In benign tertian infections the relapse rate after quinine alone is usually high (70 per cent) and some special measures should certainly be adopted.

Following the line of thought started by Acton who showed that quinine acted best in an alkaline substratum, Sinton advocated the following routine procedure in the treatment of relapsing benign tertian malaria.

The two mixtures he used were :—

<i>Mixture A</i>			<i>Mixture B</i>		
R Sodii bicarbonatis	g. lx		R Quininae sulphatis	..	g. x
Sodii citratis	..	g. xl	Acidi citratis	..	g. xx
Aquam ad	..	℥i	(or acidi sulph. dil. xx)		
			Aquam ad	..	℥i

Course.—Give calomel in divided doses, *i.e.* 6 quarter-grain doses at half-hour intervals at night, and magnesium sulphate at 6 o'clock in the morning, ℥ss to ℥i : at 7-30, 9-30 and 11-30 a.m. give one dose of mixture A, followed by a dose of mixture B at 12 o'clock; at 6 o'clock give a dose of mixture A, followed half an hour later by a dose of mixture B.

From the 2nd to 5th days inclusive give three times during the day a dose of mixture A, followed half an hour later by a dose of mixture B.

On the 6th and 7th days give a dose of mixture A, followed half an hour later by one of mixture B, twice during the day.

This makes a total dose of 180 grains of quinine. Totaquina may be substituted for quinine without detriment to the treatment and where economy is to be considered this should always be done.

Quinine plus plasmochin.—A very marked further reduction in the relapse rate in benign tertian malaria can be obtained by the addition of plasmochin to the quinine. The following dosages are recommended; the results obtained with each of these courses are about the same, but in either case the patients should be kept under observation for signs of intolerance to plasmochin.

Plasmochin 0.02 gramme *plus* quinine 10 grains twice a day,

or plasmochin 0.01 gramme *plus* quinine 10 grains thrice a day, for seven days.

Atabrin and atabrin plus plasmochin.*—Better results have been obtained with atabrin alone than with quinine alone, but, even with atabrin, plasmochin can be added with advantage in benign tertian infections.

Atabrin 0.1 g. thrice daily, plasmochin 0.02 g. once a day for five days—given together or separately.

There is considerable evidence to show that the combination of these two drugs enhances the toxic action of each, and patients should therefore

*The writer has never seen any ill-effects from these combinations, but recent experience of others seems to indicate that serious ill-effects are commoner than was previously supposed, even when the drugs are given separately. The writer would therefore emphasize the precaution that they should be given only when the patient is under strict supervision, preferably in hospital, that this combination should only be used for the specific purpose for which it is designed, namely the treatment of relapsing benign tertian malaria, and that it should only be resorted to when quinine is not available.

be kept under strict observation while these combinations are being administered. Many workers take the view that it is better to give atebirin alone for five days and then to give plasmochin in doses of 0.01 gramme twice daily for another five days. If the drugs are given in this way the danger of toxic symptoms is undoubtedly less, but the course of treatment is prolonged.

Arsenic is a valuable adjuvant in the treatment. This can be given in the form of some arsphenamine preparation in three doses at 7-day intervals between two courses of cinchona febrifuge or quinine and alkalies, or as liquor arsenicalis added to a 'tonic' mixture given after the specific anti-malarial course.

(5) **Gametocyte destruction in the cause of general prophylaxis.**—This does not in any way help the patient, for gametocytes can never again become asexual forms as long as they remain in the blood, but if they are taken up by a mosquito they develop and the infection may be transmitted to others. It is therefore only in the interests of *general* prophylaxis that attempts should be made to destroy gametocytes.

It is in this capacity that plasmochin, and the closely allied drug cilonal, are unique. No other drug that we know will destroy the gametocytes of malignant tertian, but this can be effected by a very small dose of plasmochin, 0.01 gramme, twice a day for three days. It may be given for the last three days of the quinine or atebirin treatment or after the course has been finished.

Mass treatment with plasmochin is a prophylactic measure suitable only in isolated communities, but it is essential that every single member of the community, particularly the infants, should be treated, and this is rarely possible (*see p. 112*).

A comprehensive course.—We have considered treatment of malaria under the five headings separately, but in most circumstances one will naturally wish to achieve more than one of these objectives; in fact, except for the first which cannot be achieved with any drug we have at our disposal, one will often wish to achieve all of them. That is to say, one will want to treat the clinical attack, to ensure that the condition does not recur, either as the result of a relapse or of a re-infection, and finally to prevent the patient being a source of infection to others; for this, the following routine course should be given :—

Quinine or totaquina, gr. x, three times a day with plasmochin 0.02 gramme (or $\frac{1}{3}$ grain) once a day, for seven days, followed by quinine or totaquina, gr. x, daily, or 0.2 gramme atebirin in a single dose on two consecutive days each week; in either case the last-mentioned dosages must be given as long as prophylaxis is to be maintained.

Army routine treatment of malaria.—The army has adopted the mnemonic '2525' for the treatment of malaria.

2 days of quinine gr. x, *t.d.s.*

5 days of atebirin 0.1 g., *t.d.s.*

2 days interval.

5 days of plasmochin 0.01 g., *t.d.s.*

There is reason, besides easy memorizing, in this. The patient will probably be in the 'field' when the attack starts and atebirin is only issued to hospitals*.

*I am informed that now, in some circumstances, even unit issued with mepacrine (atebirin), and that another reason for this is—quinine is reputed to control fever more rapidly than atebirin; the writer has never been satisfied that this is the case.

He may possibly be admitted to hospital later, when a full course of atebirin can be given. The 2-day interval is a concession to the theory that atebirin and plasmochin interact toxically, and the five days of plasmochin to the belief that the addition of the latter reduces the chances of relapse; this certainly applies in the case of benign tertian infection, and in malignant tertian it destroys the gametocytes, but, for this purpose, it is only necessary to give 0.01 g. of plasmochin twice daily for three days.

The 'austerity' course of quinine.—Since Java has been lost, there is naturally a serious shortage of quinine; it is therefore necessary to reconsider dosage, so that the best may be obtained out of the quinine stocks available. As noted above, the tendency in recent years has been towards giving smaller doses of quinine with the object of encouraging the development of the patient's natural resistance, while controlling the worst clinical symptoms. Medical authorities in India have therefore suggested that, as a routine course in hospital and civil practice, the quinine or cinchona febrifuge dosage should be reduced to gr. v, *t.d.s.* for five days, a total dosage of 75 grammes per attack.

It will not be possible to gauge the effect of this modification in dosage for some time; it is possible that the relapse rate may be increased, but it is believed that a greater benefit will be conferred on the community as a whole by this procedure than by giving a longer course to a smaller number of persons.

Toxic Effects

The cinchona alkaloids.—*Cinchonism* is the word used to indicate the mild toxic symptoms that follow the administration of these alkaloids, namely headache and a 'fullness' of the head, buzzing in the ears, and deafness. Cinchonism is largely responsible for the unpopularity of the cinchona alkaloids amongst patients. The extent to which different individuals suffer from cinchonism varies very considerably; in this respect the personal factor is more important than the drug factor, though some alkaloids, *e.g.* cinchonidine, and some salts, *e.g.* quinine hydrobromide, are reputed to cause less cinchonism than others.

Taken in large doses all these alkaloids have toxic actions, and even in moderate doses these effects may be apparent in susceptible individuals. As we have noted above, quinidine is a heart depressant, and cinchonine is apt to irritate the gastric and intestinal mucosa and cause vomiting and diarrhoea. The other crystalline alkaloids may produce the same effects but are much less likely to do so. Quinine given in large doses produces albuminuria, and this complication was at one time comparatively common, but is seldom seen now that the large doses of quinine have been abandoned; it will seldom occur if not more than 30 grains a day are given. Amblyopia, usually the result of large doses, may occur with a moderate dose. Temporary blindness sometimes accompanied by mental confusion has also been reported in susceptible individuals.

Finally, some individuals have an idiosyncrasy towards quinine and even a very minute dose of quinine will precipitate toxic symptoms; these include anaphylactic-like symptoms, urticaria and other rashes, local swellings, and hæmorrhages, as well as those already mentioned. Such patients can sometimes be desensitized by commencing with fractional doses and increasing the dosage very gradually, but, as alternative drugs are now available, it is seldom necessary to do this. The occurrence of quinine hæmoglobinuria, as distinct from blackwater fever, is now questioned, but the writer recently saw an undoubted case; this is another example of personal idiosyncrasy.

In the treatment of the toxic effects caffeine is the only drug of much value; this can be given as a subcutaneous injection, caffeine citrate, gr. 4, or five grains by mouth, preferably before the quinine is administered.

(Otherwise, symptomatic treatment is indicated, *e.g.* large doses of bicarbonate of soda or if necessary adrenaline for the vomiting.

Plasmochin.—The common mild toxic effects are cyanosis, gastric pains, slight jaundice, and more rarely hæmoglobinuria. These were commonly experienced when the large therapeutic doses of 0.09 gramme daily were given; with the therapeutic doses now recommended, especially as the drug is usually given with quinine which appears to have an antagonistic action, even these mild symptoms are rare; there are however cases of individual idiosyncrasy where these symptoms follow small doses. The cyanosis results from the formation of methæmoglobin.

There is still considerable misunderstanding amongst members of the medical profession regarding the place of plasmochin in malaria treatment, and instances of gross overdosage are not uncommon. The following incident illustrates the dangers of self medication :—

A planter living in a malarious district took a tablet of quino-plasmochin (containing 0.01 gramme of plasmochin) daily for two years as a prophylactic measure (not one hopes on medical advice, as it would be useless in this capacity); during this time he remained quite free from fever. When he obtained a fresh supply he was given tablets of plasmochin simplex by mistake; these tablets contained 0.02 gramme of plasmochin. He noticed that the tablets were smaller than those he had been taking and proceeded to double the dose, that is, to take two tablets at a time. He then had an attack of malaria, and by way of treatment he decided to take his two tablets three times a day. Thus, in the place of the original 0.01 gramme daily, he was now taking 0.12 gramme of plasmochin, and he continued to do this until he became seriously ill.

Atebrin.—Although toxic effects do occasionally follow atebrin administration, there is much misunderstanding on the subject.

Almost without exception all drugs that are therapeutically active are toxic. Toxicity must therefore be considered relatively—the dose administered and the person to whom it is administered. There is strong evidence that atebrin given in the ordinary therapeutic doses is not toxic to the ordinary individual, though occasionally a patient who has some idiosyncrasy to the drug will show special symptoms.

This personal idiosyncrasy may be found with any drug but the practitioner naturally wants to know how often these susceptible individuals are likely to crop up in his practice.

General experience indicates that mild symptoms occur in about 3 per cent of those treated with the ordinary effective course, and that an increase in the individual or total dosage will lead to a greater frequency of such incidents. With ordinary dosage, the more severe instances will probably occur less than once in a thousand cases, and the really serious ones not once in ten thousand. Therefore, it will be seldom that the practitioner, who keeps to the ordinary dosage, will encounter in his whole experience anything but the mildest by-effects and these should not deter him from using a valuable drug. At the Calcutta School of Tropical Medicine, though we have had patients who have come into hospital for treatment on account of suggestive symptoms following the administration both of atebrin and of plasmochin, we have treated many hundreds of patients with atebrin during the last 10 years and in none of these have any serious symptoms followed.

The actual and reputed by-effects can be classified as follows :—

(i) *The result of a misconception, e.g.* yellow colour mistaken for jaundice.

(ii) *Symptoms really due to malaria itself, e.g.* gastro-intestinal or cerebral disturbances, hæmoglobinuria.

(iii) *Symptoms following overdosage*, as noted below in (iv) and (v) in—(a) patients who have undertaken treatment themselves, (b) patients who have been first treated by a doctor and then continued treatment themselves, and (c) patients whose doctors have wrongly advised them through ignorance.

(iv) *Mild by-effects which cannot harm the patient but about which the doctor should warn him*, e.g. (a) yellow discoloration—suggesting that the drug is not being properly excreted; this should also act as a warning signal, and (b) a 'knocked-out' feeling (general lassitude) due to reduction in hæmoglobin which is dependent on destruction of parasitized red cells (it does not occur in the uninfected person receiving atabrin).

(v) *Personal idiosyncrasy following ordinary dosage*, e.g. gastric pains, headaches, giddiness, anorexia, hæmoglobinuria, epileptiform fits, and psychosis.

Hæmoglobinuria is more usually associated with plasmochin administration.

Epileptiform fits have been reported—the consequence was not serious and evidence that they were actually caused by the drug was not complete. Cases of temporary psychosis are reported from time to time: a series of such cases were reported from Malaya (Neave-Kingsbury, 1934) where an enormous number of people have been treated by the drug. The author has seen only two instances in his personal experience.

(vi) It is known that plasmochin in large doses will give rise to symptoms (*vide supra*); it is suggested that the addition of plasmochin, in even small doses, increases the toxicity of atabrin.

General management of a case.—Malaria not being a disease of the modern metropolis but of the tropical jungle, recommendations to treat it by putting the patient to bed in a high-ceilinged well-ventilated room with a night and a day nurse in attendance may not seem very reasonable to the practitioner who has to treat the vast majority of his patients where they lie, stand, or even march, and where the specific treatment will be the only thing that he can possibly afford to consider. Nevertheless, the message that such recommendations convey is the right one, namely, that the potentialities for serious development of the malarial attack should always be kept in mind, and that therefore the patient should, whenever possible, be put to bed and watched carefully for serious developments. The room should be darkened, and in the choice of clothing and bedding the drenching sweats that the patient may suffer should be remembered. If circumstances do not permit these to be changed frequently, then only flannel clothing and woollen blankets should be allowed; on the other hand, if proper nursing is available these are unnecessary and will not add to the patient's personal comfort.

The diet should be light, and during the febrile period only fluids should be given; these should include plenty of glucose. The bowels should be kept open daily by giving six quarter-grain doses of calomel at half-hour intervals, followed by salts in the morning at first and subsequently salts in the morning when necessary. Aspirin and caffeine can be given for headache, or, if these fail to relieve it, phenobarbitone.

There is a popular theory that quinine should not be given at the height of the fever; there is no foundation for this, and specific treatment should be given immediately its administration is decided upon. Unless there is serious doubt about the diagnosis, the result of the blood examination should not be awaited. At one time, a great deal was made of the

necessity of administering the drug at the moment of sporulation, in order to catch the merozoites before they find their way into new corpuscles; the evidence that the parasites are more susceptible at this stage is not very convincing and certainly nothing should be sacrificed in order to give the drug at this particular moment; better results will be obtained by maintaining a regular dosage.

A return to full diet can be allowed immediately the fever is controlled, and, in fact, in the majority of cases from this point no further restrictions need be imposed on the patient, but much will depend on other factors, *e.g.* his age, the severity of the attack and the degree of debility he has suffered and the conditions to which he proposes to return; he may also have to continue his specific treatment (*vide supra*) and he must be informed regarding the possibilities of relapse.

If the patient has become at all anæmic during the attack—this is by no means always the case—the appropriate treatment should be given for the anæmia. In the ordinary attack of malaria there has been no actual loss of iron from the body, but nevertheless, possibly because of previously-existing iron deficiency so common in the tropics, iron given in large doses will usually improve the blood picture. The rational treatment is with liver extract, either by injection or by the mouth, and autolysed yeast products, such as marmite. In the absence of facilities for accurate blood examination, treatment for both microcytic, *i.e.* iron, and macrocytic anæmia, *i.e.* liver extract and marmite, should be given. A useful prescription for the former is:—

R Ferrous sulphate ..	grains 6	Liquor arsenicalis ..	minims 2
*Quinine sulphate ..	" 2	Dilute sulphuric acid ..	" 5
Magnesium sulphate ..	60	Peppermint water to	one ounce

To be taken three times a day.

* Omit at present in interests of economy.

The treatment of the special case.—It is scarcely possible to lay down hard-and-fast rules and to provide for all contingencies in the treatment of any disease, and this is particularly true of malaria with its great variety of manifestations; special mention must however be made of the treatment of the **pernicious** forms of malaria, the cerebral and the algid forms. In both these forms prompt action is necessary to save the patient's life and, even when facilities for blood examination are present, it may not be advisable to await the confirmation of the blood film; this does not apply if there is any real doubt about the diagnosis as it only takes a few minutes to make and stain a film. In any case, the film should be taken for later examination if immediate examination is not possible. Oral administration will probably be out of the question and some parenteral method will have to be adopted. Atebrin, in the form of the soluble atebrin musonate, is the drug of choice; this should be given intravenously in a dose of 0.125 gramme and repeated twice at one hour's intervals, or intramuscularly as a single dose of 0.375 gramme. (The large dose is often given intravenously, but a few instances of ill-effects have been reported.)

If atebrin, or its equivalent, is not available, the next choice is quinine, 10 grains (0.6 gramme) of some soluble salt dissolved in 20 c.cm. of saline and given intravenously. Finally, if for any reason (*e.g.* the absence of suitable syringe or of sufficient sterile solvent, or the difficulty of finding a suitable vein) the quinine cannot be given intravenously, it must be given intramuscularly, with the necessary precautions (*vide supra*). This dose should be repeated within a few hours if the acute symptoms do not subside.

It is possible that the circumstances may necessitate the parenteral route being used on the following day, for example, if vomiting occurs or persists, but by the third day it will, in almost every case, be possible to change to oral administration. This should be done at the earliest possible moment and the usual course completed.

Chronic malaria.—The treatment to prevent relapses has already been discussed, and when relapses do occur, or the patient suffers a succession of infections, the treatment must be repeated. The patient with chronic malarial cachexia may, or may not, respond to the ordinary course of treatment, and in most cases there will only be a slight diminution in the size of the spleen. In these circumstances, the treatment known as Ascoli's treatment is certainly worth trying; this consists in the daily intravenous administration of adrenaline. The doses must be very small, or serious reactions will occur; the first dose should be 1/100th of a milligramme, that is, 0.01 c.cm. of the usual 1 in 1,000 solution, and to measure this accurately, even with a tuberculin syringe, dilution with normal saline will be necessary. Subsequent doses should be 2/100ths, 3/100ths, etc. up to 1/10th; this last dose should be repeated up to about 15 times, making a total of 25 injections. In a suitable case the effect on the spleen is remarkable, and sometimes a spleen that was two inches below the costal margin will disappear under the ribs in two or three minutes, to return to its previous size in about half an hour. In course of time the diminution in size becomes permanent. The Ascoli treatment should be combined with oral administration of the cinchona alkaloids to obtain the maximum and most permanent results.

Another method for reducing the size of the spleen is the intramuscular injection of sterile fat-free milk, at least 12 injections, from 2 c.cm. to 10 c.cm., twice weekly.

The pregnant woman.—The importance of giving the pregnant woman adequate treatment cannot be over-emphasized. Whenever possible it is best to give atabrin, or its equivalent, but failing this, quinine can be given in modified dosage. A dose of 20 grains of quinine will sometimes precipitate labour (quinine is used for this purpose) but doses of 5 grains are safe, and the full course should be given in 5-grain doses. It is a common obstetric practice in highly malarious countries to give a course of anti-malarial treatment in every case shortly before labour is due, as a routine measure even in the absence of evidence of malaria infection.

PROGNOSIS

This must be considered from a number of different points of view, the immediate response to treatment, the chances of relapse, the immediate mortality, the indirect mortality, and the general effect on the health of the individual.

Prognosis will depend on the species and strain of parasite, the nutrition of the patient and his previous experience of malaria, the treatment given, and complications.

There are considerable differences in the virulence of the malaria strains in different localities; no general rule can be applied, but in peninsular India the strains are generally of low virulence, whereas in the Himalayan districts they may be much more virulent. The first attack of malaria is always likely to be serious, and the seriousness usually decreases with each successive attack, provided the attacks are well spaced; further, an attack is likely to be more serious in a newcomer to a locality, as he is not immune to *local* strains.

PREVENTION

When treatment is immediately available, no one should die as the result of malaria alone, but when a patient is first seen already unconscious, his chances of recovery will be in the inverse ratio to the length of time that he has been unconscious and of the further delay in administering treatment.

In the partially immune, adequate treatment will usually control the attack within 48 hours, that is to say, given first during one paroxysm in a single tertian infection, it will control the next paroxysm, but in the non-immune it will usually fail to do so, though controlling subsequent paroxysms. Malignant tertian infection will often resist treatment for four or five days (*see* figure 16); if the fever lasts longer than five days, the efficacy of the treatment should be investigated (*see* p. 101), and/or the diagnosis reviewed.

The highest rate of immediate mortality is caused by *P. falciparum* (malignant tertian) infection; it is particularly fatal in the infant and young child, and in the pregnant woman. *P. vivax* (benign tertian) and to a less extent *P. malariae* (quartan) infections will seldom prove immediately fatal, even when no treatment is given.

On the other hand relapses after adequate treatment are less common in malignant tertian malaria.

Benign tertian malaria is probably little short of malignant tertian in the seriousness of its indirect effects, especially on account of its marked tendency to relapse; about 70 per cent of primary attacks relapse after an ordinary course of quinine.

Quartan infections fall between malignant and benign tertian, both in the severity of the attack and in the liability to relapse. Kidney complications are said to be most common in quartan malaria, but they also occur in malignant tertian.

Anæmia is more likely to follow *P. falciparum* infections. The failure of the blood picture to return to normal rapidly is usually an indication that some infection still remains and that a relapse may be expected. However, when the patient is in a state of malnutrition, liver extract will often be required to bring the blood count back to normal, even though the infection has been eradicated.

In a healthy well-nourished person who receives adequate treatment, convalescence is short and return to full activity may be expected within a week or ten days; should frequent attacks or relapses occur at short intervals, the period of convalescence will be considerably lengthened, and still further so, if the attacks are complicated by any bowel disease that interferes with nutrition.

P. ovale infections are always mild and seldom relapse.

PREVENTION

To appreciate the possibilities of malarial prophylaxis the reader must turn back to page 64 and consider the factors that determine malaria incidence. If the cycle can be broken or even sufficiently weakened at any point malaria will be prevented.

The methods by which the cycle may be broken can be discussed under the same four headings :—

- A. *The malaria parasite.*
- B. *The mosquito vector.*
- C. *Man.*
- D. *The links between B and C.*

about by interference with natural drainage by the building of railways, roads, etc., or may consist of irregular collections of water in dead rivers or in river beds during the drier seasons of the year.

(v) *The control of larval breeding in large essential collections of water*; lakes, reservoirs and tanks, rivers, irrigation channels and streams, drainage channels, and rice fields.

In the case of water collections of the first three groups, it is not absolutely essential first to consider whether they are the source of mosquito vectors, though the information will be of value for the other reasons, because in any case they will breed other mosquitoes which may carry other diseases and are at the least a cause of annoyance to man. The methods of dealing with these will usually be obvious. Where they cannot be eliminated, they should be dealt with in other ways; wells and cisterns must, for example, be kept covered, or the water emptied periodically, in many cantonments in India, a 'dry day' is instituted once a week; on this day all uncovered collections of water must be emptied.

Water collections of the last two groups present the real problems of malaria control by anti-larval measures about which so much has been written; it will only be possible here to enumerate some of the methods that have been adopted, and readers must refer to the many useful books on this subject for details (*e.g. Covell, 1941*).

The methods of eliminating the large collections of water or controlling breeding in them are almost without exception expensive, and it is therefore first essential to make sure that these potential breeding places are actually the source of mosquito vectors and are an important factor in the malaria incidence in the locality. It will be necessary to find out what species breed in these waters at different times of the year, whether these species are recognized vectors, and finally whether they do in this particular locality actually carry malaria; this latter can be found out by catching and dissecting a large number of mosquitoes at the right time of year. This common-sense procedure of utilizing accumulated knowledge, to which has been added the results of local investigation, regarding which mosquito species do actually carry malaria, and of only attacking these is often given the status of a new principle in malariology and referred to as **species control**. It will usually be found that one species of mosquito only is the important vector in a locality, and if this is the case all one's resources can be directed towards making conditions unsuitable for this particular species. Nine times out of ten this measure will be successful in reducing the malaria; on the tenth occasion it may make conditions more suitable for another vector and thereby defeat one's object. This is where the expert's superior knowledge will come in, but where nature is concerned no one is omniscient.

For some of the very worst set-backs in anti-malaria campaigns, the responsibility goes to world-famous malariologists who have come to a new country and, without studying local conditions sufficiently or listening to the advice of less famous local malariologists, have tried to apply methods that they had previously employed with success in other countries. It is therefore essential to make a very careful study of local conditions before giving any advice on larval control methods. Each country in the world presents its own particular problems, and if one cannot learn from some local malariologist, one should make a special study of the books or papers based on local experience, although there are many useful books in which the general principles are discussed.

There are numerous methods of draining unnecessary collections of water, and circumstances will dictate which of these is likely to be the most fruitful. Or it may be cheaper to treat the breeding places with larvicides. Permanent waters, rivers, streams, etc., may be made innocuous in a number of different ways by physico-chemical means, *e.g.* pollution, changing the saline content, silting, or muddying; by physical means, *e.g.* removing marginal vegetation (anchorage for larvæ), agitating the surface, increasing the rate of flow, intermittent irrigation, flooding, periodic sluicing or the reverse—stagnating, shading or letting in the light; by biological means, *e.g.* changing the flora and fauna, introducing larvivorous fish, or deterrent aquatic vegetation (largely theoretical); or by poisoning the larvæ, or their food supply, with oil, chemical poisons, *e.g.* paris green or copper sulphate, or vegetable larvicides, *e.g.* pyrethrum or derris.

Anti-imago measures.—The principle of this method of control is not simply to reduce the number of mosquitoes, nor even to kill the infective mosquitoes, but to *prevent the local malaria vector from becoming infective by shortening its average duration of life*. The most striking demonstration of its effectiveness is that in all cases when spraying is carried out properly the infectivity rate among mosquitoes immediately drops to *nil*.

Recently, much more attention has been paid to this method, particularly in Europe and cooler countries where the mosquito enters a house and tends to remain there for long periods if left undisturbed, and where it is much easier, in closed rooms, to destroy them. However, this method has been used extensively in hotter climates, even under conditions where it is more difficult to close the rooms on account of the much more open nature of the habitations, and considerable success has been claimed. It is particularly applicable to private houses, barracks, and offices, but can be applied to the huts of the poorer inhabitants. It is also employed usefully in public conveyances, railway carriages, omnibuses, and aeroplanes.

The methods of destruction employed are swatting, trapping, fumigating and spraying, the last-named usually being the method of choice.

Spray-killing of adult mosquitoes is now recognized to be one of the major methods of control in anti-malaria campaigns. It is the only one of the anti-imago measures of real practical importance. It is the only measure which can have an *immediate* effect on the course of a malaria epidemic which has already started; it is the only anti-malaria measure which is universally popular; and it is one of the few anti-malaria measures which is likely to have a success in combating rural malaria. It might be said that, next to site selection and in special circumstances drug prophylaxis, it is the most important of all anti-malaria measures for troops operating under modern war conditions.

Covell considers that the Punjab epidemics provide an excellent opportunity for spray-killing of adult mosquitoes. The epidemic units that are organized to meet these epidemics and distribute quinine should be equipped also with sprayers and supplies of pyrethrum spray. Energetic spraying should immediately bring the epidemic under control and the consequent saving of anti-malarial drugs would more than compensate the outlay in sprayers and pyrethrum spray. If the value of the method could be established, village communities might be induced to keep their own sprayers to meet an emergency.

The most effective sprays have a basis of kerosene and the majority contain pyrethrum; there are many proprietary brands, but a useful and not expensive spray may be made from 19 parts of kerosene and one part of concentrated (2 per cent) extract of pyrethrum.

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There are certain advantages in a spray with a watery base; the main ones are lower cost and non-inflammability. The only disadvantage, other than the difficulty—which can be overcome—of preparing a suitable emulsion, is the fact that the droplets are heavier, and therefore the 'mist' does not rise as well as that from the kerosene spray. Russell, Knipe and Rao (1942) have recommended the following spray :—

Twenty pounds of pyrethrum flowers are extracted with 12 gallons of white kerosene. This will make 10 to 11 gallons of concentrated extract; the extract is mixed with water in the proportions of 1 to 7, and 23 grammes of sodium lauryl sulphate (or 'Gardinol') are added for each gallon of emulsion.

Technique of Spraying*

All apertures should be closed as far as possible before spraying, and should remain closed for 20 minutes thereafter. It is, however, usually impossible to do this completely, in which case it is necessary to use rather more of the spraying solution. It is more economical in the end to use a greater quantity of spray, rather than to waste time in stopping up apertures with sacking, etc. Even when the structure sprayed consists of a thatched roof without sides, numbers of mosquitoes can be killed by directing the spray upwards into the thatch. Before spraying the inside of a hut, the outside should be systematically sprayed under the eaves. The sprayer should in all cases be directed upwards.

Period of spraying.—Systematic spraying should commence a fortnight before the malaria season is expected to start and should be continued throughout the transmission period.

Time of spraying.—Mosquitoes almost invariably feed during the night. *A. minimus*, for instance, usually feeds between midnight and daybreak. After feeding, the mosquito remains in a sluggish condition during the early stage of digestion of its blood meal. It is therefore advisable to commence spraying in the early morning as soon as after daybreak as possible.

Frequency of spraying.—The efficacy of the method is in direct proportion to the frequency with which it is carried out. Where the percentage of infection among the vector species of anophelines is low, good results have been obtained by spraying once a week. In very malarious areas, however, where the infectivity rate among the local mosquitoes is high, it is necessary to spray at least twice, preferably thrice, a week, and at the height of an epidemic the rule should be to spray as often as possible.

Amount of spray required.—This is about half an ounce per 1,000 cubic feet, which is about the size of the average one-roomed coolie hut. Allowance must also be made for spraying other suitable anopheline shelters, such as cattle-sheds and store-rooms.

Sprayers.—Power-driven sprayers are the most effective, and are also the most economical in consumption of spray, in labour and in time of spraying. The apparatus used is identical with that employed for the spray-painting of motor cars, etc. The following models have been found suitable :—

1. De Vilbiss portable petrol-driven power sprayer, type NH-616, 1/ H.P., mounted on trolley, cost about Rs. 605/-.

2. De Vilbiss portable electric (universal) sprayer, type NC-615, 1/4 H.P., mounted on trolley, cost about Rs. 330/-.

Excellent results can also be obtained by the use of hand sprayers, although there is no type at present available which is at the same time effective in operation, durable, easy to operate, and economical in consumption of spray.

Pyrethrum cultivation

As a supplementary measure to the recommended policy of growing sufficient cinchona in India for her own needs, the cultivation of pyrethrum should be undertaken on a large scale, but Government must foster this industry, or disaster may overtake it as it did the cinchona industry half a century ago. At the present, some encouragement might well be given by the guaranteeing of a minimum price for pyrethrum flowers, as India is at present far from supplying her own needs. For spray-killing to be applied on a large scale, the flowers must

* From a circular issued by the Malaria Institute of India.

be marketed at not more than 6 annas a pound; at this price, cultivation should provide a good profit.

Pyrethrum will grow in many places in India, and so far the Indian-grown flowers have been found to give a higher yield of pyrethrin than the Japanese flowers, though not as high as the Kenya plants.

There are probably unexplored **biological methods** of destroying adult mosquitoes, but none so far suggested has proved of any value whatsoever. A classical example was the erection of a bat tower or 'belfry' to encourage bats which were reputed to feed on mosquitoes; this failed because (i) the bats refused to live in the tower in any numbers, and (ii) those which did, it was found, did not feed on mosquitoes.

C. Man.—The elimination of man would break the malaria cycle. Short of this drastic procedure, it is however possible to take some action under this heading.

Increasing immunity.—Immunity is seldom complete, but if a community is by previous experience of malaria well immunized against a particular strain—the term *salted* is used in this connection—it will mean that the adult in the community seldom suffers from an infection heavy enough to cause a febrile reaction or to lead to the formation of any considerable number of gametocytes; he will thus not himself become a casualty nor will he be a prolific source of infection to the mosquitoes in the locality. In this way, immunity acts as a brake on the intensity of the malaria incidence in any community and any measure that raises this immunity is an anti-malarial measure, just as, conversely, anything that lowers it is a malariogenic factor.

A method of malaria control, mainly practised in Italy, is known as **bonificazione** or **bonification**; this includes increasing the immunity of the population by raising their standard of living and treating the sick, as well as other methods of malaria control, such as irrigation and drainage (see figure 23).

Other measures of control under this heading will include the careful **selection of labour forces**, so that immune populations are not mixed with non-immune, and children are excluded as far as possible.

The question of employment of *salted* labour is a very complicated one. Some employers of labour advocate it strongly and others criticize it. The ideal labour force in a malarious district consists of the

locally-recruited labourers that are partly immunized against all local strain. Labourers recruited from a malarious district may be partly, but will not be completely, immune to local strains, and further they will bring their own strains with them to which local or other imported labourers are not immune (*vide* p. 73). Therefore, if labour from more than one place has to be recruited, their sleeping quarters should be kept some distance apart.

D. The links between the mosquito (B) and man (C).—Provided that the mosquito vector can be kept away from man, malaria will not occur. The methods of preventing, or reducing the chances of, this contact may be considered under the headings *general* and *personal*.

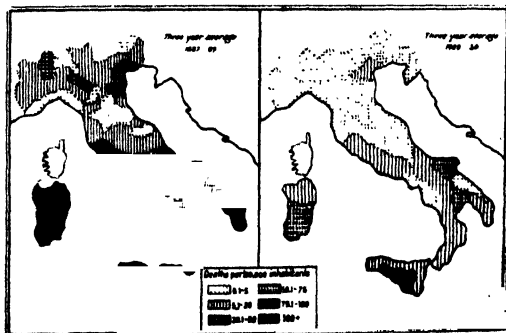


Figure 23 : Decrease in mortality from malaria in Italy over a forty-year period. (Hackett, 1937.)

General.—In the choice of sites of towns, villages, settlements, coolie lines, camps or even houses, the question of the proximity to uncontrollable mosquito-breeding grounds, as well as to uncontrollable human reservoirs of infection, should always be considered. Whenever possible the opinion of an expert malariologist should be obtained. In the past, millions of pounds could have been saved by this simple precaution, and mistakes are still being made. Unless he has made a special study of malariology and had some personal experience, a medical officer should refuse to express an opinion on a matter of this kind, and, whenever any considerable amount of money is involved, he will be well advised in any case to insist on the opinion of an expert malariologist being obtained.

Small bodies of men, hunting parties, prospectors and engineers, or 'commando' troops, going into malaria-infected country should be warned to avoid native villages for their temporary night halts as they would a plague-stricken village; they should also view with equal suspicion any clearing in bush or jungle which has obviously recently been the site of an encampment.

Where the village or residence is already established there are some biological methods of interception that have been advocated; these include the planting of alleged deterrent vegetation, *e.g.* neem and eucalyptus trees, castor-oil plants, lavender and clover, and the use of cattle to deviate the attentions of the mosquitoes from their human sources of blood supply, *i.e.* zooprophylaxis (*see* p. 70 : Zoophilism). In practice, all these biological methods have proved disappointing.

Another measure is the **screening** of barracks, hospitals, and houses. In some countries this is practised extensively and its popularity is increasing; it must always be considered, whenever it is practicable, as an additional measure. Dr. D. P. Curry, who has directed the mosquito control work for many years in the Panama Canal Zone, recently wrote, 'in spite of all our sanitation, we still must insist on screened living quarters, and screened offices for those persons who must work at night'. It does not add much to the cost of a building to include screening in its construction. Combined with systematic spray-killing, screening may be considered a major method, in places where more comprehensive methods of malaria prevention are impracticable. It is however necessary that the building should be a well-constructed one and for this reason the method has its limitations. Copper-wire netting is the most generally useful, except near the sea; it should be 14 mesh, 20 to 30 gauge (S.W.G.); this gives an aperture of about 0.056 inch, which will keep out all mosquitoes in ordinary circumstances and does not interfere too much with the entrance of fresh air.

Other points in the construction of buildings are the avoidance of dark corners in which mosquitoes can lurk during the day and the provision of electric fans; the latter is perhaps verging on the personal methods of prevention.

The **personal** methods of protection include the use of repellents for smearing over the uncovered parts of the body, the spraying of ankles with one of mosquito-killing sprays (*v.s.*), mosquito boots or other simpler means of protecting the legs, *e.g.* a pillow-case tied round the knees whilst sitting at table, veils and gloves, and mosquito nets.

Innumerable repellents have been suggested from time to time, but recent investigations in India have shown that pyrethrum is more effective as a repellent than any other substance so far tested.

Covell recommends the following formula :—

Extract of pyrethrum (2 per cent)	20 c.cm.
Oil of citronella	5 "
Gum tragacanth powder	4 grammes
Water	80 c.cm.

Note.—If a stronger extract of pyrethrum can be obtained, it should be used. If the European tragacanth is used, the quantity should be 5 to 6 grammes.

Granett (1940) has recommended a liquid repellent containing

Diethylene glycol monobutyl ether acetate	} 65 per cent
" " mono-ethyl ether	
Ethyl alcohol, maize oil, and perfume	35 "

which is effective and pleasant to use.

Mosquito nets 'should be 25/26 mesh of 30/s cotton'. These trade terms will mean little to the ordinary man; they are arrived at by fantastic methods of calculation with which the reader need not burden his memory. They do *not* mean that there are 25 holes to the inch, linear or square; actually, a net of this specification has about 12 holes to the linear inch and 150 to the square inch.

Similarly, the mosquitoes must be prevented from feeding on an infected person, and in a hospital or other institution the patient suffering from malaria should always be made to use a mosquito net, as a measure of protection for the community.

Amelioration of the effects of malaria.—In certain circumstances it has been found that the practical difficulties of preventing malaria are so great that preventive measures are scarcely worth attempting. In these circumstances the question of organized treatment to ameliorate the effects of malaria should be considered. Bonification, referred to above, is really a measure of this nature, though it may achieve mosquito control as a side line.

In many places in India there is little hope of eradicating malaria and the next best measure is to provide cheap or free treatment for the individual sufferer, not with any hope of actually eradicating the disease, but in order to mitigate the damage that the infection does. This is especially true in the epidemic areas in the Punjab where for a short time during the year conditions may be extremely favourable for transmission, and where anti-larval measures would be impossible or prohibitively costly. By studying climatic conditions that precede these epidemics, sanitarians have learnt to foretell epidemics and, with the help of special epidemic units, now arrange for the mass treatment of the population by free distribution of cinchona alkaloids and by other means. The possibilities of combining this treatment campaign with spray-killing of mosquitoes is discussed above.

Malaria Surveys.—Before undertaking or recommending any procedure designed to control malaria, it is essential that one should have all the obtainable data at one's disposal, and in nearly every case some form of malarial survey will have to be undertaken. By a malaria survey one ascertains the extent to which malaria is present in the locality, or, if a large area is involved, in different parts of that area, how it affects different sections of the population, the time of year when it is most prevalent, what are the vectors, what are their sporozoite rates and where they breed, and in fact all that can be ascertained about the epidemiology of malaria under the various headings under which it has been discussed above.

The extent of malarial endemicity can be judged from the 'parasite rate' or the 'spleen rate', or preferably both. To find out the **parasite rate**, thick and thin films will have to be taken of a representative group of the population, and examined by the methods described above; from this examination the infestation rate and the average parasite count can be calculated, of the whole and of different groups of the population, but there are many refinements in this type of work and the reader is referred to one of the books devoted to this subject (*e.g.* Covell, 1939).

The calculation of the **spleen rate** has similarly been reduced to a fine art (Covell*, *loc. cit.*), but there are simpler methods that give invaluable information. The spleen rate is usually taken from children between the ages of two and ten years, as it has been shown that between these years the spleen's reaction to malarial infection is more constant than at other ages. The children should be lined up against a wall and the sizes of their spleens ascertained by palpation. The children are placed in five classes according to the sizes of their spleens; class I, not palpable—o; class II palpable but not beyond the costal margin—p; class III, up to three-fingers' breadth below the costal margin—+; class IV, larger than this but not to the navel—++; class V, reaching the navel or beyond—+++. The important point is the percentage that shows palpable splenic enlargement; this is known as the 'child spleen rate'. As far as India is concerned, different areas have been classified according to the child spleen rate, as follows :—

Healthy areas—below 10 per cent.

Areas of moderate endemicity—from 10 to 25 per cent.

Areas of high endemicity—between 25 and 50 per cent.

Areas of hyperendemicity—*constantly* 50 per cent or over.

In conclusion, the successful control of malaria requires a very wide knowledge and a very open mind. Practical experience, even in one locality, is useful, but, unless the knowledge thus gained is applied intelligently, it becomes mere stupid prejudice and will be a handicap rather than a help. Every possibility should be considered before any one method of control is decided upon. The experience in malaria control of those on the spot should never be ignored, but it should be examined critically to make sure that the methods have not become unintelligent routine.

The economic aspect will always be paramount in this imperfect world. One's first thoughts must be, how much will it cost and will it pay? An accurate answer to the first half of the question should be given, but for the second a long view may have to be taken. A government should be satisfied with a promising long-term policy, even if it is likely to be ten years before the good effects are felt; a commercial concern naturally expects a quicker return though they may be content to wait a year or two; but on the other hand, a commander of an army, or an engineer in charge of the construction of a railway, road or bridge, may have little interest in what happens next year and only be concerned with next week or next month.

* Christopher's method has many advantages, including the important one of allowing for differences in the size of the children, and is very easy in practice, though from the description it appears complicated. It consists in marking the 'apex' of the spleen, taking two measurements only, the nipple-umbilicus and the umbilicus-apex, with a centimetre tape measure, and applying a correction obtained from a table. For further details reference should be made to Government of India, *Health Bulletin* No. 14.

MALARIA THERAPY

The origin of this form of treatment was the observation that, though syphilis is as common in most malarious countries as it is in the temperate zones, neuro-syphilitic conditions are comparatively rare in the former. The first observation on this subject was made by Wagner von Jauregg, a Viennese physician, in 1887, though it was nearly 30 years later before any general attention was directed to this subject by the publication of the results of his practical trials in the treatment of general paralysis of the insane by malaria.

This form of treatment attracted a very great deal of attention in Europe, and in England a 'mosquito farm' was organized under the auspices of the Ministry of Health for the purpose of conveying malaria infection, easily and safely, to those who were to be treated by this measure.

Besides being a very successful form of treatment—about half the patients suffering from general paralysis thus treated were considerably improved by the treatment—it provided us with a very valuable opportunity for studying experimentally certain aspects of malaria transmission.

The infection may be transmitted by the agency of laboratory-bred mosquitoes, directly by their bite or by dissecting out the salivary glands and inoculating the sporozoites, or by the injection of infected blood (*vide supra*). In the latter case, 2 to 5 c.cm. of defibrinated blood from a patient with malaria is inoculated intramuscularly into the subject to be treated. Care must be taken that the donor has no other transmissible disease, *e.g.* syphilis, or a malaria infection other than the one that one wishes to transmit.

Plasmodium vivax is the infection of choice, but, where the patient is, or has become, immune to all the available strains of *P. vivax*, it may be permissible to inoculate *P. malariae* or even certain benign strains of *P. falciparum*. Both *P. ovale* and the simian parasite, *P. knowlesi*, have also been used.

In malarious countries where more than one species of malaria parasite is prevalent, it is almost—in fact one might say quite—impossible to be certain that the proposed donor has only one species of parasite in his blood, and therefore very great vigilance must be exercised, when the patient develops malaria, to identify the species.

An example of this difficulty occurred recently in the author's experience. A patient with an apparently pure benign tertian infection was admitted to hospital as a source of malarial infection for another patient with tabes dorsalis. His blood was examined repeatedly for about a week by means of thick-film, thin-film, and cultural methods, and only benign tertian parasites were found. However, on the day that his blood was to be given to the tabetic patient a quartan parasite was found, so that the inoculation was postponed while further examinations were carried out; a few more quartan parasites were found but the infection was still mainly benign tertian. As the infection was showing signs of dying out, inoculation was not delayed further. Twelve days after the inoculation the tabetic patient developed fever which was found to be due to a heavy *malignant tertian* infection, and within a day or two very energetic anti-malarial treatment had to be given to save his life.

The patient should be allowed to have 8 to 12 paroxysms before the infection is terminated by anti-malarial treatment. If the rigors are too severe and occur daily, the severity of the attack can be controlled by neo-arsphenamine; a dose of 0.05 to 0.10 gramme is usually sufficient (Winckel, 1941). The infection can be finally terminated by 5 grains of quinine three times a day for five days.

This form of treatment has been largely superseded by other forms of hyperthermic therapy, for example, by mechanical means or by the administration of pyrogenic drugs; this is particularly so in America.

REFERENCES

- ACTON, H. W. (1910) The rationale of quinine prophylaxis. *Indian Med. Gaz.*, **45**, 283.
- BOYD, M. F. (1941) A symposium on human malaria with special reference to North America and the Caribbean Region. Publication of the American Association for the Advancement of Science. No. 15.
- BOYD, M. F., and STRATMAN-THOMAS, W. K. (1934). On duration of infectiousness in Anophelines harbouring *Plasmodium vivax*. *Amer. J. Hyg.*, **19**, 539.
- BOYD, M. F., STRATMAN-THOMAS, W. K., and KITCHEN, S. F. (1936). On duration of infectiousness in Anophelines harbouring *Plasmodium falciparum*. *Amer. J. Trop. Med.*, **16**, 157.
- CHRISTOPHERS, S. R. (1925) .. Two malarial surveys connected with industrial projects in certain very highly malarious localities in India. *Ind. Jour. Med. Res.*, **13**, 343.
- COVELL, G. (1939) *How to do a malaria survey*. Health Bulletin, No. 14. Malaria Bureau, No. 6. Fourth edition. Manager of Publications, Delhi.
- Idem* (1941) *Malaria control by anti-mosquito measures*. Thacker, Spink and Co. (1933), Ltd., Calcutta.
- DARLING, S. T. (1909) Transmission of malarial fever in the canal zone by anopheles mosquitoes. *J. Amer. Med. Assoc.*, **53**, 2051.
- DAS GUPTA, B. M. (1939) .. Malarial infection in the placenta and transmission to the foetus. *Indian Med. Gaz.*, **74**, 397.
- EDWARDS, F. W. (1932) Diptera, Family Culicidae. *Genera Insec* Fasc. 194. L. Desmet-Verteneuil, Brussels.
- FIELD, J. W. (1941) Further note on method of staining malarial parasites in thick blood films. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **35**, 35.
- FIELD, J. W., NIVEN, J. C., and HODGKIN, E. P. (1937). The prevention of malaria in the field by the use of quinine and atabrin. *League of Nations : Bull. Health Organization*, **6**, 236.
- GRANETT, P. (1940) Studies of mosquito repellents, I. Test procedure and method of evaluating test data. *J. Econ. Ent.*, **33**, 563. Abstract (*Rev. App. Ent.*, Ser. B, 1941, **29**, 65).
- HACKETT, L. W. (1937) *Malaria in Europe*. Oxford University Press, London.
- HAGGIS, A. W. (1941) Fundamental errors in early history of cinchona. *Bull. Hist. Med.*, **10**, 417 (referred to in *Brit. Med. Jour.*, 1942, *i*, 299).
- D'HERELLE, F. (1924) *Immunity in natural infectious disease*. Williams and Wilkins Co., Baltimore.
- JAMES, S. P. (1926) *Anopheles maculipennis*, three months' infective. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **19**, 278.
- JAMES, S. P., NICOL, W. D., and SHUTE, P. G. (1936). Clinical and parasitological observations on induced malaria. *Proc. Roy. Soc. Med.*, **29**, 879.
- KIKER, C. C., and BREEDLOVE, H. E. (1941). Mosquito-proofing for malaria control from the standpoint of construction costs. *Amer. J. Hyg.*, Sect. C, **34**, 95.
- KINGSBURY, A. N. (1934) .. Psychoses in cases of malaria following exhibition of atabrin. *Lancet*, *ii*, 979.

- KITCHEN, S. F. (1941) .. The infection in the intermediate host : symptomatology, falciparum malaria. 'Human Malaria', p.196. Publication of the American Association for the Advancement of Science. No. 15.
- KITCHEN, S. F., WEBB, E. L., and KUPFER, W. H. (1939). The influence of malarial infections on the Wassermann and Kahn reactions. *J. Amer. Med. Assoc.*, **112**, 1443.
- LAMPRELL, B. A. (1940) .. Quinine and atebirin in the control of malaria. *Indian Med. Gaz.*, **75**, 266.
- LLOYD, R. B., NAPIER, L. E., and SMITH, R. O. A. (1925). The 'blood meal' of *Phlebotomus argentipes* identified by precipitin antisera. *Ind. Jour. Med. Res.*, **12**, 811.
- LOWE, J. (1934) .. Studies in untreated malaria. *Indian Med. Gaz.*, **69**, 16.
- MAYNE, BRUCE (1930) .. Tests on the effects of Coumarin on the life of the mosquito and the malaria parasite. *Ind. Jour. Med. Res.*, **17**, 963.
- MOST, H. (1940) .. Malignant malaria among drug addicts : epidemiological, clinical and laboratory studies. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **34**, 139.
- NAPIER, L. E., BUTCHER, D., and DAS GUPTA, C. R. (1932). Field experiments with atebirin and plasmochin. *Indian Med. Gaz.*, **67**, 186.
- NAPIER, L. E., and DAS GUPTA, B. M. (1932). Atebrin : a synthetic drug for the treatment of malaria. *Indian Med. Gaz.*, **67**, 181.
- NOCHT, B., and MAYER, M. (1937) .. *Malaria : A Handbook of Treatment, Parasitology and Prevention*. John Bale, Sons and Curnow, Ltd., London.
- RUSSELL, P. F., KNIPE, F. W., and RAO, T. R. (1942). A water emulsion of pyrethrum extract for spray-killing adult mosquitoes. *Indian Med. Gaz.*, **77**, 477.
- SINTON, J. A., and GHOSH, B. N. (1934). Studies of malarial pigment (hæmozoin). Part I. Investigation of the action of solvents on hæmozoin and the spectroscopical appearances observed in the solutions. *Rec. Mal. Survey, India*, **4**, 15.
- STRICKLAND, C., and BAIRD, S. Y. (1939). Early infantile malaria. *Brit. Med. Jour.*, **i**, 979.
- TROPP, C., and WEISE, W. (1933) .. Untersuchungen über die Ausscheidung von Atebrin durch Harn und Fäzes. *Arch. exper. Path. u. Pharmacol.*, **170**, 339.
- WINCKEL, C. W. F. (1941) .. Neoarsphenamine to manage course of fever in therapeutic malaria. *J. Amer. Med. Assoc.*, **116**, 2660.

BLACKWATER FEVER

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Definition.—Blackwater fever is a special manifestation of malaria, characterized by hæmoglobinuria.

The pathology and the clinical picture in this condition are so characteristic and so different from those of the ordinary malarial attack that it is justifiable to consider it as a separate disease entity, though it is now generally accepted that plasmodia are the sole causal organisms.

Historical.—The main historical interest is that although malaria has been known for twenty-five centuries, with the exception of some doubtful references in Hippocratic medical writings, there is no reference to the blackwater syndrome in medical literature until a little over a century ago, when Boyle (1831) referred to it in his *Fevers of West Africa*. Scott (1939) draws attention to the fact that the literature of blackwater fever has shown a marked national grouping; about the middle of the century, writers reported the disease in Madagascar and in other French possessions in Africa, after another decade the Greeks took up the subject, and these are followed in turn by Italian, American, Dutch (Java), German (1890), and eventually British medical writers.

This late historical appearance of the disease has been used to support various claims regarding its ætiology, for example that it must be a disease *sui generis* or at least caused by a special plasmodial strain, and alternately that it must be due to quinine because quinine came into more general use about the time of the appearance of the disease in medical literature. In view of our knowledge of the epidemiology of blackwater fever, it seems to the present writer that the increase of blackwater fever at the beginning of the last century was associated with the widespread foreign invasion of tropical territory that occurred at this time, and that beyond this the observation does not point to any special ætiological factor.

EPIDEMIOLOGY

Blackwater fever occurs only in highly endemic malarious countries (or amongst persons who have lived in such countries) and its seasonal incidence is always correlated with the season of highest malaria incidence, so that its epidemiology is the epidemiology of malaria, with some special features.

Geographical distribution.—As it occurs in nearly all the intensely malarious countries in the world, no separate map is necessary; it does not, however, occur further north than 40°N. or further south than 20°S. In Europe it is most prevalent in Greece and Macedonia and in southern Italy; along the north African coast as far east as Tripoli, throughout tropical Africa, and in Madagascar; in Palestine and Syria; in the southern states of the U.S.A., in Mexico, Panama, the West Indies, and the northern countries of South America; and in India, Burma, Malaya, the East Indies, Siam, French Indo-China, and southern China.

In India, the worst blackwater fever areas are in the Dooars and Terai (at the foot of the Himalayas), Assam, the Chittagong hill tracts, Santal Parganas, Chota Nagpur, and the Madras Presidency, and in Burma in the North and South Shan States.

Whilst these are the localities where the patient acquires his predisposing tendency to blackwater fever, the attack may develop in some non-malarious country; it is quite common, for example, for those returning from the East to be attacked in London.

Local distribution.—It occurs mainly in areas where malignant tertian malaria is endemic throughout the year. In India, and in many other countries, it is prevalent where more civilized races come into close contact with primitive peoples, that is to say, on the borders of jungle tracts. In places it also has a local distribution that does not seem to be solely explained by high malaria endemicity, for in other equally malarious districts it does not occur; this has led to the suggestions, (a) that in some local carrier species of mosquito, the malaria parasite undergoes a change which endows it with special toxic properties, or, alternatively, and in the writer's opinion more probably, (b) that some hæmolytic strain of malaria parasite is prevalent locally. 'Blackwater fever houses' have also been reported; these might add support to the above theories, but it has usually been possible to explain them on the grounds of their close proximity to prolific mosquito-breeding sites and/or reservoirs of infection.

Individual incidence.—In blackwater fever areas, the disease is very rare amongst the local natives, but occurs amongst foreigners; in India, it is common in Europeans and in Indians from the cities. It seldom occurs earlier than one year after the subject's arrival in an endemic area, and is less common after four years' residence except amongst those who have had a previous attack.

People of all ages and both sexes may be attacked.

ÆTIOLOGY

The ætiological factors must be considered under two headings, (A) *predisposing*, and (B) *precipitating*. ♦

Of the predisposing factors, (i), (ii) and (iii) are essential, and (iv) and (v) important additional factors. The incidents that may precipitate an attack can be placed in three groups; one alone is sufficient but there may be a combination of precipitating factors.

(A) *Predisposing factors*.—(i) A plasmodial infection is the first essential. The disease is nearly always associated with malignant tertian infections, but instances have been reported where apparently pure benign tertian or pure quartan infections have given rise to blackwater fever.

(ii) Absence of established immunity to all local malaria strains, such as is acquired by indigenous inhabitants of a locality.

(iii) Previous subjection to intense malarial infection over a period of at least a year.

(iv) Irregular and inadequate treatment of these attacks.

(v) A previous attack of blackwater fever; this is evidence of individual susceptibility, for about 10 per cent of blackwater fever subjects suffer a second attack.

(B) *Precipitating factors*.—(i) Quinine administration: this has a double action, as it stimulates the action of the reticulo-endothelial cells to destroy parasites and incidentally red cells, and quinine itself, especially as an acid salt, also has a slight hæmolytic action. The other anti-malarial drugs may act in the same way, but are not so frequently reported as the precipitating factor, possibly because, as in the case of atabrin, the main action of the drug is a direct one on the malaria parasite itself.

(ii) Cold (*cf.* paroxysmal hæmoglobinuria), fatigue (increase of sarcolactic acid), alcohol, arsphenamine and certain other toxic drugs, and trauma.

(iii) X-ray applications to the spleen, which stimulate the hæmolytic cells of the reticulo-endothelial system.

The mechanism of hæmolysis.—The exact physiological process by which old and worn-out red cells are removed from the circulation is a question not yet finally settled, but it is probably an intracellular, rather than an intravascular, process, as little unchanged hæmoglobin can be found in the plasma of the general circulation in the normal subject. In malarial infection, with the intravascular bursting of the rosette, red cell debris is thrown into the circulation and stimulates the formation of anti-bodies including hæmolysins and probably lecitholysins which all play their part in the destruction of the invading parasite and incidentally of a very large number of red cells; lecitholysins which reduce the protecting blood cholesterol assist the latter process. Repeated attacks work up the sensitivity of the reticulo-endothelial tissues to this hæmolysin production; there is a sudden excessive stimulation and these sensitized tissues respond by an explosive production of hæmolysin which causes the 'hæmoclastic crisis' of blackwater fever. The excessive stimulation may be brought about by a particularly heavy malarial infection, possibly by a new strain of parasite against which the patient has little immunity, or, even in the presence of an ordinary infection, by the taking of quinine, which, we know, acts by stimulating the reticulo-endothelial tissues, or by subjection to

cold which assists the action of the hæmolysin already formed (cf. paroxysmal hæmoglobinuria).

As a result of this hæmoclastic crisis, an enormous quantity of oxyhæmoglobin (much of which is reduced to methæmoglobin) is thrown into the circulation (hæmoglobinæmia); the reticulo-endothelial cells convert a large amount of this into bilirubin but are unable to cope with this great excess and much of the hæmoglobin remains in the circulation, and is then excreted by the kidneys (hæmoglobinuria), which are damaged in the process. The amount of bilirubin in the blood is also well above the normal, the liver cells are unable to excrete the excess, it is deposited in the tissues, producing jaundice, and, being present in the blood in amounts above the kidney threshold (hyperbilirubinæmia), this too is excreted in the urine (bilirubinuria).

Theories regarding the cause of blackwater fever.—Even if we accept the description given above as the mechanism of the attack, it does not really explain why it occurs in some people and not in others. One suggestion is that there are certain biological strains of malaria parasite that lead to the production of a particularly active hæmolysin or lecitholysin; in favour of this are certain observations in the epidemiology of the disease mentioned above (e.g. the close association with certain places and particularly with jungle tracts), and the established fact that there are considerable differences in the virulence of different strains of malaria parasite, but against it is the occurrence of blackwater fever in therapeutic malaria—a few instances of which have been reported—where the virulence of the strain used is known. The alternative suggestion, that a benign strain might undergo some biological change during transmission by certain species of mosquito, would also be negated by the last observation, and otherwise lacks positive supporting evidence.

Some years ago the writer tentatively put forward two suggestions; these were based on both epidemiological and experimental evidence (Napier and Campbell, 1932). The first was that rapid passage through a series of susceptible hosts raised the virulence of a previously normal strain of malaria parasite, and the second, somewhat contradictory to the first, that the virulent strains of plasmodium which are harboured by the immunized people of jungle tracts, when transmitted to non-immunes (non-immune to that particular strain), caused a virulent infection. In the experiments on which these theories were based, by passage of the Simian plasmodium, *Plasmodium knowlesi* (later named as such) from a monkey of the *Silenus irus* species, in which it was dormant and overshadowed by a *P. inui* infection, through a series of *Silenus rhesus* monkeys, we produced a virulent infection associated with hæmoglobinuria* in the latter species (and incidentally drew the first attention to this plasmodium species, which has played such an important rôle in experimental malaria ever since).

There is little support for the former theory, but the latter dovetails in with the general theory enunciated above.

Other theories that have been put forward have either been disproved or died through lack of support. These include the theory that it is the result of acidosis enhanced by giving acid salts of quinine, or the excessive formation of sarco-lactic acid by muscular exertion; this theory is weakened by the observation that acidosis is not constantly present in blackwater fever. That it is a pure quinine intoxication has now been disproved by the occurrence of blackwater fever in people who have not taken quinine, so frequently that this theory can have few supporters. The finding of

* This hæmoglobinuria is not strictly comparable to blackwater fever, as it is not associated with any hæmoclastic crisis, but is simply the result of excessive destruction of red cells by the plasmodium infection, possibly combined with a low kidney threshold for hæmoglobin in the host.

a spirochætal infection in blackwater by one or two observers has not been confirmed, nor has any other specific organism been found, though there are some who still consider that it is a disease *sui generis*.

In the writer's opinion the 'phenomenon' of blackwater fever requires no explanation beyond that already outlined in the previous paragraphs, if allowance is made for varying individual susceptibility.

PATHOLOGY

Morbid anatomy.—This is basically the same as that of malaria, but there are in addition certain special changes. As in malaria, the pathological changes are brought about by the pigment and debris from the malaria parasite and destroyed red cells, by the strain placed on the organs of katabolism and excretion from the sudden extra load of which they have to dispose, and probably by the malaria 'toxin'.

In blackwater fever, the most characteristic and extensive changes are in the kidneys. The free hæmoglobin in the blood passes through the glomeruli and reaches the tubules where, the environment being more on the acid side, acid hæmatin is precipitated, and the tubules become blocked.

The kidneys are large and dark; the tubules are blocked with brown debris and hæmoglobin casts, and there is cloudy swelling and degeneration of the tubular endothelium. The liver is stained an intense yellow (hæmosiderin), and there is central necrosis of the parenchyma cells. The gall-bladder is filled with thick viscid bile. The spleen is enlarged and almost black (hæmozoïn pigment) on section; there is general endothelial proliferation and there are areas of focal necrosis in the malpighian corpuscles.

Blood.—The cytological changes will depend on the severity and stage of the disease. Again, basically, they will be the same as those in malaria. The anæmia may however be severe and it is not unusual for the red cell count to drop by 1 or 2 millions in a matter of a few hours as the result of a single attack. At this stage the anæmia will be normocytic but later there are signs of active regeneration, a marked reticulocytosis, and the anæmia is usually on the macrocytic side, to a greater extent than can be accounted for by the reticulocytes present. There is no evidence of an increased fragility of the red cells. There is a marked increase in the percentage of large mononuclear cells, most of which are histiocytes.

Parasites are by no means always found in the peripheral blood at the time the patient comes under observation, but an investigation in Africa showed that they were present in the peripheral blood in 73 per cent of cases on the day before the attack, in 47 per cent on the day of the attack, and in 23 per cent on the day after the attack.

In a series of 20 cases in northern Bengal, Bhattacharya (1941) reported finding parasites in the blood in six out of ten cases in which there had been no previous quinine treatment.

Biochemically, there is oxyhæmoglobinæmia and methæmoglobinæmia; the proportion of the latter tends to increase, being at first 1 : 3 and later 1 : 10, and a third form of hæmoglobin derivative, methæmalbumin, that is produced by the action of hæmatin with the plasma protein, appears in the blood (Fairley, 1941).

There is marked hyperbilirubinæmia in severe cases, the indirect van den Bergh test indicating an amount as high as 40 mg. per 100 c.cm. of blood.

The blood urea rises as high as 450 mg. even in non-fatal cases and in cases of renal failure this may be higher. The cholesterol content of the blood is considerably reduced. The alkali reserve may be as low as 30 c.cm. CO₂.

Urine.—When the oxyhæmoglobin and methæmoglobin reach the level of the kidney threshold, they are excreted in the urine; this takes on the colour of a light red wine, which deepens to a rich port-wine colour and eventually to the dark brown of stout or porter; as the patient recovers the colour of the urine lightens to a light brown and finally a yellow, which may persist in the urine for many days. The urine is markedly acid. If it is shaken, the presence of hæmoglobin is shown by a pink foam.

The test for albumin shows a heavy cloud.

In severe cases bile is present but this is usually masked by the hæmoglobin. Methæmalbumin is not excreted by the kidneys and does not therefore appear in the urine.

Microscopically, there is much brown debris and hæmoglobin casts, but there are few red cells.

The fæces may show pleocholia for a few days.

SYMPTOMATOLOGY

Prodroma.—Mild febrile attacks associated with a yellow discoloration of the sclerotics or frank jaundice are sometimes noticed for a day or so before the real attack, but as a rule the onset occurs with dramatic suddenness.

Onset.—Sometimes the first sign of the disease is that the patient finds his urine bright red; usually, however, the syndrome supervenes during an apparently ordinary attack of malignant tertian malaria; there is headache, very severe prostration with pain in the kidney region, nausea, and vomiting, and then the patient notices that his urine is coloured red.

Bhattacharya (*loc. cit.*) reported the first appearance of hæmoglobin in his 20 cases as follows :—

Day of fever			No. of cases			Day of fever			No. of cases		
1st day	3			4th day	5		
2nd day	3			5th day	2		
3rd day	7			TOTAL	20		

The course of the disease.—There is usually a single severe hæmoclastic explosion, all the damage being done in a matter of a few hours, but there may be a series of hæmolytic crises, in which case the prognosis is poor. The temperature is high at first but tends to be very irregular later, the pulse is very rapid, and the blood pressure is low; later, the blood pressure may rise with the onset of renal failure. The headache, nausea, vomiting, hiccough, and pains in the loin and epigastrium continue. Dyspnoea, due to anoxæmia as the result of red cell destruction, may be marked. The patient may show signs of collapse, with restlessness and an anxious expression, pallor, shallow breathing, and a rapid thready pulse.

Meanwhile the urine will have passed through the stages of port-wine colour and be almost black, but in severe cases anuria will set in, and,

though it is not uncommon for urinary secretion to commence again, even after 48 hours, azotæmia ('uræmia') as the result of continued anuria is a common cause of death. Even polyuric cases may prove fatal.

The spleen is usually markedly enlarged and tender (but may be temporarily reduced during an attack as a result of the expulsion of reserve blood), the liver is tender and the gall-bladder may be felt; jaundice appears early, on the second day, and is usually unaccompanied by itching.

Recovery may be rapid, or on the other hand the symptoms may increase and the patient die of heart failure, or cerebral symptoms—irritability, delirium and coma—may appear; in such a case he usually shows early signs of collapse, the breathing becomes Cheyne-Stokes in character and death soon follows.

A marked degree of anæmia, which is usually macrocytic, and general debility are common sequelæ. In some cases blood regeneration takes place very rapidly without any specific treatment, but when the anæmia is definitely macrocytic, it may necessitate vigorous hæmatinic treatment (*vide infra*).

Relapses are common.

Clinical types.—The recognized special types are (a) the mild (more-or-less symptomless hæmoglobinuria), (b) the fulminating, (c) the continuous (in which repeated hæmolytic crises occur), (d) the anuric, and (e) the hæmorrhagic.

DIFFERENTIAL DIAGNOSIS

The conditions from which blackwater fever has to be distinguished can be grouped under the following headings:—

(a) **Hæmoglobinuria**, caused solely by the taking of quinine or plasmochin (the existence of this condition is now questioned), 'march' hæmoglobinuria, paroxysmal hæmoglobinuria (an interesting condition dependent on the incompatibility of an individual's plasma and red cells due to the presence of a special hæmolysin, the action being precipitated by cold, usually locally applied cold), nocturnal hæmoglobinuria (Marchiafava-Micheli syndrome), syphilitic hæmoglobinuria, hæmoglobinuria caused by poisons such as potassium chlorate or carbolic acid, snake bite, and as a result of specific sensitiveness to certain dietary substances, an example of which is 'favism', a condition simulating blackwater in other symptoms and caused by eating uncooked broad beans (*Vicia faba*) in excess (Luisada, 1941).

Certain drugs and other substances may produce a red coloration in the urine, which could be mistaken for hæmoglobin, for example, beetroot, cochineal and, amongst the drugs, amidopyrin, phenolphthalein, and prontosil-rubrum.

Hæmoglobinuria is also imitated as a means of malingering (in India, *pan*, commonly chewed by Indians, particularly women, added to the urine makes a fair semblance of hæmoglobinuria). The final test for hæmoglobin is by means of a spectroscope; the hæmoglobin bands are easily recognized. This can be done with a pocket spectroscope.

(b) **Hæmaturia**, due to various local causes, oxaluria, new growth, stone, etc., yellow fever, hæmorrhagic diathesis and other conditions where hæmorrhages occur from mucous membranes.

(c) **Jaundice**, due to any cause but especially yellow fever, or Weil's disease; in both these conditions it develops later and tends to progress.

TREATMENT

General principles.—The patient should be treated and nursed on the spot, and moving avoided as far as possible; he should be kept warm and if possible provided with a night and a day attendant; the acidosis should be counteracted vigorously; and he should *not* be given quinine.

As the acute stage is likely to be a short one, the patient need not be pressed to take food, and, if he demands it, fluid of low protein content only should be given. The fluid intake should be maintained at a high level and at least 6 pints of fluid given daily. Thirty grains of bicarbonate of soda can be added to a pint of barley water or fruit juice and water without making it unpalatable. Additional bicarbonate can be given in a mixture, and if intravenous saline is indicated, 150 grains of sodium bicarbonate to the pint should be added; at all costs the urine must be kept alkaline to prevent precipitation of the hæmatin and the consequent damage to the renal tubules. Glucose should be given by the mouth *ad lib.*, and some workers prefer intravenous glucose, 5 per cent solution, to intravenous bicarbonate as they report that it also helps to reduce hæmolysis.

Anti-malarial drugs.—In the majority of cases there are no parasites in the peripheral blood at the time the patient is seen after the attack, and in these circumstances no anti-malarial drug is necessary. If parasites are still present atebirin in the usual doses (*see* p. 101) should be given.

Symptomatic.—For **anuria**, if intravenous therapy fails, hot fomentations or dry cupping should be applied to the loin, hot colonic washes given and finally the bladder filled with warm citrate saline (2 per cent sodium citrate in normal saline) and the patient allowed to empty the bladder after a few minutes; this often starts a reflex secretion of urine.

Sodium sulphate, 1.89 per cent of the anhydrous salt in distilled water, given intravenously by the drip-feed method, up to a litre, should be tried, if the above methods fail.

The diuretics that are most likely to be of value are caffeine and sodium benzoate given by intramuscular injection in doses of 4 grains, or caffeine citrate gr. iii or diuretin gr. x three times daily given by the mouth.

Vomiting can sometimes be stopped by giving the patient ice to suck; if not, 1 c.cm. of adrenaline diluted with an ounce of water should be given by mouth but if this and other simpler means of controlling vomiting fail, an injection of morphia (1/10 grain) and hyoscine (1/200 grain) may be given.

For cardiac stimulation, camphor in oil, cardiazol, and coramine are the drugs of choice.

As a purgative, calomel should be given in divided doses ($\frac{1}{4}$ grain half-hourly up to $1\frac{1}{2}$ grains).

'Specifics'.—A large number of specifics for the treatment of black-water fever have been advocated. Many of these have acquired a considerable local reputation, though usually without any scientific basis. A good example of such a drug is the extract of *Vitex peduncularis*. How this is supposed to act has never been clearly defined by its advocates; it has no effect on a malarial infection, but recently a special extract from this plant has been prepared which has been shown to possess definite anti-hæmolytic properties *in vitro* (Gupta *et al.*, 1942).

Another such specific is extract of *Cassia beareana*; this does not grow in India and recently the extract of an allied species *Cassia fistula* has been tried in this country, with *apparent* success.

A line of treatment more recently introduced is with cortin, or its synthetic equivalent, desoxycorticosterone acetate, 25 mg. immediately and 5 mg. 4-hourly, combined with vitamin C in maximal doses intravenously or intramuscularly, and cholesterol 15 grains 4-hourly by the mouth. Even in this case, the exact rationale is not clear and it is doubtful if cholesterol taken by mouth increases the blood cholesterol appreciably, but the writer has seen uniformly satisfactory results with this routine during the last few years. Again, however, no scientifically controlled series of experiments of sufficient number to carry any weight have been reported upon.

Blood transfusion and other hæmatinic treatment.—Transfusion has been used freely in England in anæmic and asthenic cases, but has not been so successful in the acute hæmolytic stages of the disease in the tropics. It should be avoided in anuric cases, but in other cases, where the patient is suffering from anoxæmia after a crisis, transfusions of cross-matched whole blood up to 400 c.cm. in the first instance are certainly worth considering; they must always be given slowly. Oxygen will always be helpful at this juncture.

After the acute stage has subsided, as there has been an actual loss of hæmoglobin in the urine, there will be some iron deficiency which should be made up, but liver extract usually causes a more dramatic improvement in the blood picture. Marmite should be given, and continued for some weeks if possible.

Diet.—Diet should be fluid and of low nitrogen content during the acute stages; it should be increased gradually but protein should be avoided for a few days. When the albumin has disappeared from the urine, a liberal well-balanced diet should be given to compensate for the serious protein losses that have accompanied the attack.

Convalescence.—A special word of warning is necessary in convalescence, as sudden heart failure is common; some physicians insist on all patients remaining strictly in bed for at least 10 days after the hæmoglobinuria has completely stopped.

PREVENTION

The prevention of blackwater fever is the prevention of malaria and the subject does not require separate discussion here (*see pp. 111–119*).

The drug prophylaxis is also the same as for malaria, but, in view of the undoubted action of quinine in precipitating an attack of blackwater fever, the question whether it is advisable to take prophylactic quinine in a blackwater fever area will naturally arise. Whenever this point has been investigated, it has been found that the disease is far less common amongst those who take prophylactic quinine regularly than amongst those who take it just when they happen to remember it, or not at all. Thorough treatment of the malarial attack, whenever it occurs, can be looked upon as a prophylactic measure against blackwater fever; for this, atebirin is probably preferable to the cinchona alkaloids, and, after a blackwater fever attack, preference should certainly be given to the atebirin group of drugs.

If the old remedy *Vitex peduncularis* lives up to its new promise, it might provide a drug that could usefully be employed prophylactically in a blackwater fever country, especially by blackwater fever subjects, whenever they feel a malarial attack coming on.

PROGNOSIS

One of the principal characteristics of blackwater fever is the great variability of the severity of the disease from place to place and from time to time in any one place; this is why the results of any particular form of treatment are so likely to be misleading. When large series are reported the death rate usually varies between 10 to 20 per cent, but in a smaller series a death rate of 40 per cent is not at all uncommon and conversely death rates as low as 5 per cent are reported.

The prognosis deteriorates with each successive attack. There is a popular saying in blackwater fever districts that 'one often recovers from the first attack, seldom from a second, and never from a third'. This is of course not true but it conveys the right message, and, as there is some evidence of individual susceptibility which is possibly enhanced by an attack, it is advisable for a blackwater fever subject to seek employment in some other locality.

REFERENCES

- BHATTACHARJEE, J. C. (1941) .. Blackwater Fever in Darjeeling Terai. *Indian Med. Gaz.*, **76**, 734.
- GUPTA, J. C., KAHALI, B. S., and GANGULY, S. C. (1942). *Vitex peduncularis*—A New Antihæmolytic Agent. *Indian Med. Gaz.*, **77**, 721.
- FAIRLEY, N. H. (1941) .. Methæmalbumin. *Quart. J. Med.*, **10**, 95.
- LUISADA, A. (1941) .. Favism : Singular Disease chiefly affecting Red Blood Cells. *Medicine*, **20**, 145.
- NAPIER, L. E., and CAMPBELL, H. G. M. (1932). Observations on a Plasmodium Infection which causes Hæmoglobinuria in Certain Species of Monkey. *Indian Med. Gaz.*, **67**, 246.
- SCOTT, H. H. (1939) .. Blackwater Fever. *A History of Tropical Medicine*, **1**, 252. Edward, Arnold and Co., London.

LEISHMANIASIS

CLASSIFICATION OF LEISHMANIA INFECTIONS

The diseases in man caused by protozoa of the genus *Leishmania* Ross, 1903, can be considered under the following three headings :—

(i) Visceral leishmaniasis, or kala-azar, in which the causal organism, *Leishmania donovani*, is spread by the blood and invades practically all the tissues in the body except those of the nervous system.

There is an infantile variety of kala-azar, and in the past the causal organism of this disease was called *Leishmania infantum*; but it is now generally considered that this latter organism is identical with *L. donovani*. Similarly, the causal organism of the recently discovered South American variety of kala-azar has been called *Leishmania chagasi*, but its distinction from *L. donovani* has not been established.

Post-kala-azar dermal leishmaniasis, in its numerous forms, is a late sequel to the generalized infection; in this condition the parasites (*L. donovani*), having disappeared from the viscera, are confined to the skin and cause non-ulcerative skin lesions unaccompanied by any general symptoms.

(ii) Cutaneous leishmaniasis or oriental sore, in which the infection is localized in the skin and causes ulcerative lesions; in this condition the infection is apparently not spread by the blood-stream, but, rarely, extension has occurred along lymphatic channels; *Leishmania tropica* is the causal organism.

(iii) Muco-cutaneous or South American leishmaniasis, or espundia, in which there is a primary invasion of the skin, as in oriental sore, followed, sometimes after the original sore has healed, by a specific ulceration of the nasal, buccal, and pharyngeal mucous membranes; the spread of infection is presumably by the blood-stream, although the blood infection has not been demonstrated in this disease; *Leishmania braziliensis* is the causal organism.

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Definition.—Kala-azar or visceral leishmaniasis (also known as black fever, Dum-Dum fever and ponos) is a fever of long duration, which occurs epidemically or endemically in certain tropical and subtropical countries, is usually associated with progressive emaciation and enlargement of the spleen and liver, and is characterized by the presence of a parasitic protozoon, *Leishmania donovani*, in the peripheral blood, in the spleen, and elsewhere in the tissues.

Historical.—In India kala-azar has been recognized as a distinct clinical entity for over a hundred years. A number of epidemics occurred in Bengal and, though it was undoubtedly confused with malaria, the frequency with which the infection failed to respond to treatment and ended fatally made the physicians of those days realize that they were dealing with a different disease. More attention was attracted to the disease when it began to invade Assam in 1875; kala-azar swept up the Brahmaputra valley in three distinct epidemic waves between this date and 1917. Some interesting examples of the dangers of partial correlations were displayed when Giles (1892), finding hookworm ova in the stools in every case, declared the disease to be ancylostomiasis, and later when first Rogers (1897) and then Ross (1899) concluded that it was a severe form of malaria, for a parallel reason. Both these infections will be found in almost 100 per cent of the inhabitants of some districts in Assam.

The position was clarified when in 1903 the causal organism, now classified as *Leishmania donovani*, was discovered almost simultaneously by Leishman in the spleen of a soldier who died in England from kala-azar which he had contracted at Dum-Dum, a military cantonment just outside Calcutta, and by Donovan in the smears made from spleen material at biopsies and necropsies.

A disease known as 'ponos', which had been recognized in Greece and other Mediterranean countries for many years, was shown to be caused by the same organism.

Kala-azar was first diagnosed in China by Aspland in 1910 and in the Sudan by Bousfield, Thomson, and Marshall (1911).

EPIDEMIOLOGY

Geographical distribution.—The disease has a widespread distribution in the Old World, and has been reported from South America, but up to now not from Oceania.

In Europe, the most heavily infected areas are in Sicily, the 'toe' of Italy, and certain Mediterranean islands. In the Adriatic, an indigenous case has been reported in Venice, and in Yugoslavia the disease appears to be comparatively common. It is prevalent along the coastal area of the provinces of Catalonia and Valencia in Spain, in Malta, and in Crete, Hydra, and other Greek islands; isolated cases have been reported from many other Mediterranean ports. At Catania 1,424 cases were diagnosed in a period of ten years, and in Hydra 39 per cent of the deaths among infants during one year were said to be due to this disease, but in most of the other places it is only sporadic in occurrence (see figure 24).

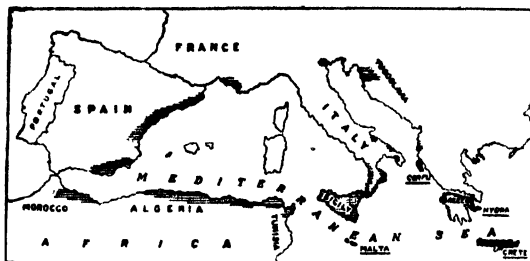


Figure 24: Map showing kala-azar distribution (shaded) in the Mediterranean area.

In the Mediterranean area the disease is confined almost entirely to infants and young children.

In North Africa, the same infantile form of the disease occurs along the Mediterranean littoral, in Morocco, Algeria, and Tunis, the incidence being highest in the last-named. There is another endemic area

in the Sudan, in Kassala and the Blue Nile district, and cases have been reported from Abyssinia, northern Kenya, and a few other places in tropical

Africa; but only in the Sudan endemic focus has there been any serious incidence of the disease; here kala-azar, which is not of the infantile type but has an age distribution comparable to the Asiatic form of the disease, came into prominence during the fighting in 1940-41 in Abyssinia and on the borders of the Sudan, and a number of Indian troops were infected.

In India, the distribution is extensive, but the limits of the endemic areas are well defined, the disease being confined to the eastern side of the peninsula. Intensely infected isolated villages have been found in the extreme south near Cape Comorin. There is a steady incidence of a few

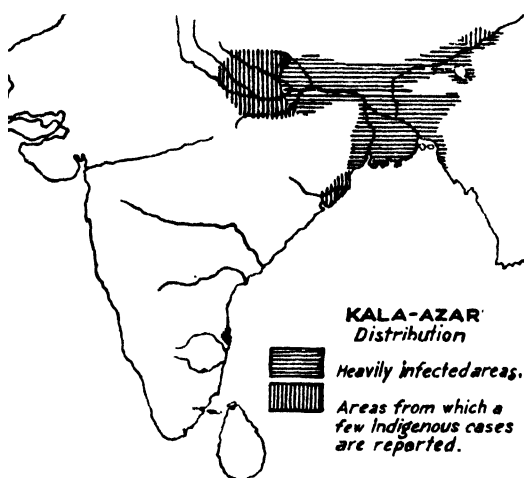


Figure 25 : Map showing kala-azar distribution in India.

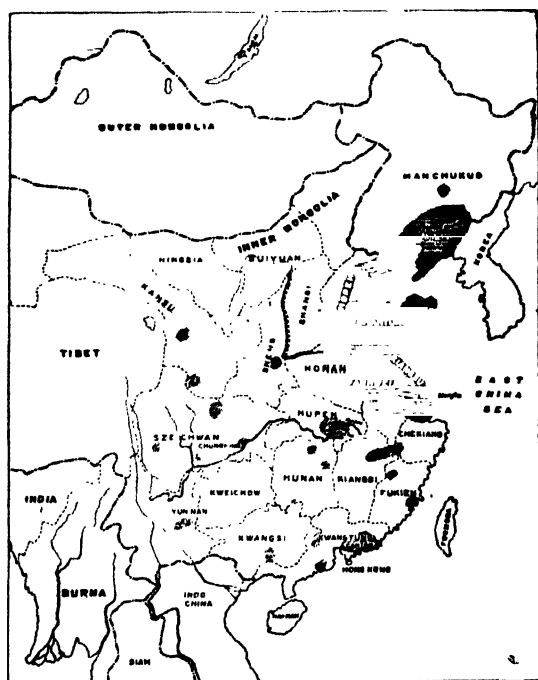


Figure 26 : Map showing kala-azar distribution in China : shaded areas.

canal in the provinces of Kiangsu, Shantung, and Chih-li up to Peiping and further north into Jehol and Fientien, in Manchuria. Cases have also been

hundred cases each year in Madras city. The coastal areas are then free up as far as the Ganges delta. The whole of the plains of Bengal are heavily infected. The endemic area spreads along the Ganges plain into Bihar, where the incidence is still high, and to the eastern side of the United Provinces as far as Lucknow, where the incidence gradually tails off, its westerly extension being checked by the dry areas. In Bihar it is confined to the Ganges valley, being limited on the north by the Himalayas and on the south by the low laterite hills of the Bihar plateau. In a north-easterly direction the endemic area extends along the Brahmaputra valley into Assam, which province is heavily infected as far as Sibsagar; at present sporadic cases only occur further east. From the main Bengal focus the endemic areas extend into eastern Bengal and Sylhet, but further extension is prevented by the high mountain ranges which divide India from Burma. It will be interesting to see whether the opening up of direct communications between India and Burma across these mountains will lead to an extension of the disease into Burma; on analogy, the writer believes that it will not (see figure 25).

In China, the endemic areas are nearly all north of the Yangtze river and are mainly along the line of the grand

reported from Mongolia. Undoubted indigenous cases have been found in a few places in western and southern China, but there is some question if the cases reported in the extreme south near Canton and in Yunan (also shown in figure 26) are really indigenous cases, in view of the extensive migrations of the population that recent events have led to.

There are endemic foci in Transcaucasia and Russian Turkestan. It has recently been shown that kala-azar is widespread in the tropical zone in South America, and a few cases have been reported from Argentina. Isolated cases have been reported from here during the last twenty years, but on the whole the reports were received with scepticism, until light was thrown on the subject by the yellow-fever viscerotomy service in Brazil and Argentina; out of 47,000 viscerotomies, leishmaniae were found in 41 specimens. Subsequent clinical investigations in some of the infected areas brought to light a few cases of kala-azar. Nearly all the leishmania-infected viscerotomy specimens and most of the clinical cases came from the north-east corner of Brazil between Para and Bahia, but a few kala-azar patients were also found in the Chaco district of Argentina. The cases were sporadic, and entirely unconnected with one another (see figure 27).

Epidemic features.—In most countries in which it exists, kala-azar is sporadic in its occurrence, but there are others, such as Bengal, where it is intensely endemic although subject to exacerbations of an epidemic-like nature. In the days before effective treatment was given, these rises and falls in incidence appear to have had a definite periodicity of about fifteen to twenty years. In an endemic area, there was usually a widespread increase in incidence over the whole area, which lasted for three or four years; then there would be a gradual fall, but the disease did not disappear, and even in the trough of the wave the incidence did not drop to less than one-third or a quarter of the incidence at the top of the wave.

The character and periodicity of these epidemic waves are probably being disturbed by the extensive treatment campaigns that have been instituted in the most heavily infected provinces, Assam and Bengal, since the beginning of the last epidemic. The last epidemic wave started in 1917 and reached its peak about 1923. On previous experience another wave is overdue by at least five years, but provincial health returns give little indication of it, except in the province of Bihar, at the periphery of the endemic area, where no treatment campaign was instituted, and here the increase in the incidence of the disease has recently alarmed the health authorities.



In individual villages or in smaller areas within an endemic area, the epidemic wave will be shorter and sharper and may be followed by a period of some years during which the disease disappears almost completely; but when the incidence is falling in one village it may be rising in another not many miles away.

There are indications that a concatenation of climatic or other factors, such as widespread distress after an earthquake or an influenza epidemic, determines a generalized increase, and that local conditions and the population factor determine the extent and duration of the incidence in the individual villages; when all the highly susceptible material, *i.e.* the children born since the last epidemic wave, is exhausted, the disease dies down. In a village in Bengal in which we studied the disease for many years 20 per cent of the population of three hundred were attacked within a period of three years, and two years later only one case occurred during the whole year.

The disease may also show a true epidemic invasion of an area. During the last half-century there have been three epidemic waves in Assam; each has carried the disease further up the Assam valley. In the part of the Assam valley adjoining the Bengal plain, kala-azar is now endemic, as it is in Bengal, but further up the valley it appears in epidemic form and seems to disappear entirely in the period between epidemics. The disease has not yet reached the extreme eastern end of the valley.

Factors determining distribution.—In India kala-azar is confined to areas below 2,000 feet, although a few isolated cases of rather doubtful origin have been reported from higher altitudes, and to alluvial soil, to areas with a high humidity, *i.e.* a mean annual humidity of not less than 70 per cent, and with a low mean diurnal range of temperature, *i.e.* not more than 20°F.; it is a disease of rural areas rather than of towns, and when it occurs in the latter it is found in old, low (one storey) and usually damp residences with small compounds in which there is some vegetation and in which fowls, ducks, or goats are kept, *i.e.* in surroundings very similar to those of the rural areas, except that in the towns there are usually organized sanitary services and good water-supplies (*see* plate IV, figures 2 and 3).

Kala-azar is a family, house, and site infection, and it was shown in Assam that even burning down a hut and re-erecting one on the same site did not check the spread of infection, but that removal of 'coolie lines' a distance of at least three hundred yards was essential.

In China also it is a disease of rural areas, but in towns, such as Peiping, there are endemic foci comparable to those in the towns in India. In the infected areas on the Mediterranean littoral, the disease is reported as occurring mainly on the outskirts of towns and villages in surroundings similar to those already described, but there the association with dogs, which are suspected as carriers in some countries, has been noted.

Seasonal incidence.—In most of the places where the disease has been studied, a definite seasonal incidence has been noted. In Bengal and Assam there is a well-defined peak in the onset curve in the winter months, but it starts to rise in the autumn, the period immediately following the rainy season (*see* figure 28); in Madras the seasonal incidence is less well defined. In the Sudan and Abyssinia, Henderson (1937) noted that the rise in the seasonal curve started in August which is the height of the rainy season. In China the early summer months and in Europe the spring are the periods of highest incidence.

Age and sex incidence.—In so far as the age incidence of the disease is concerned, the endemic areas are sharply divided into two groups. In the Mediterranean areas the disease occurs among infants and very young children, 93 per cent under the age of five years, and is rare among adults. On the other hand, in Asiatic endemic areas the highest incidence is among children between the ages of five and fifteen years. This difference in the age incidence has led some workers to regard kala-azar in the two regions as being distinct, and to use the term 'infantile kala-azar' for the disease as it occurs on the Mediterranean littoral. The age distribution, however, is the only notable point of distinction. Even in India kala-azar occurs among infants; we reported a case of an infant of less than eight months with well-developed kala-azar of about four months' duration.

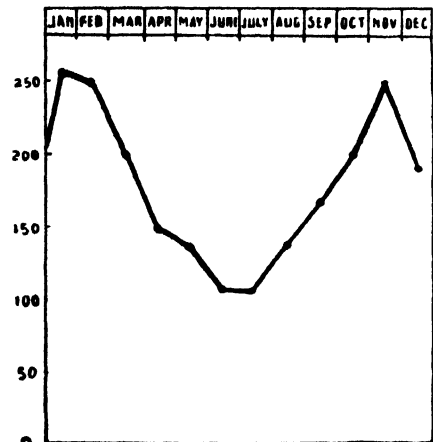


Figure 28 : Month of onset of kala-azar; based on over 2,000 cases seen in Calcutta.

The age incidences in the two sexes seem to differ slightly; in Bengal we found that the peak of the age-incidence curve was from the eighth to the tenth year in girls and from the tenth to the twelfth in boys. This is possibly correlated with the earlier maturity of females in India. Many figures showing the age incidence are available, but the following table, although based on a comparatively small number, is probably the most accurate, since the figures were collected by house to house investigation over a long period, and are not taken from hospital and dispensary returns. They are probably typical of the Asiatic endemic areas generally. The available evidence suggests that in the Sudan the age incidence is slightly higher; Henderson (1937) reported 34 per cent in persons aged 20 years or under (cf. 74 per cent in our Indian series).

Age and sex incidence of kala-azar

Age group	Males	Females	Total	Per cent per quinquennial age period
Under 5 years ..	22	26	48	12.40
5 years, but under 10 years	48	57	105	27.13
10 15	60	29	89	23.00
15 20	26	20	46	11.88
20 30	30	37	67	8.65 × 2
30 40	16	8	24	3.10 × 2
40 50	2	6	8	1.03 × 2
TOTAL ..	204	183	387	

There is no evidence that either sex is the more susceptible; most of the collected figures show a preponderance among males, but, when the errors of selection are eliminated, the difference practically disappears.

Race, caste and class.—There is also no evidence of racial or class immunity. In India, Europeans and Asiatics are equally liable to infection

when living under comparable conditions. The disease is rare among better-class Europeans and Indians living in well-built and well-ventilated houses, but it is very common among poorer-class Europeans and Anglo-Indians. In some mixed villages the disease seems to predominate among those living in the Mohammedan and Indian Christian quarters, the Hindus being comparatively free.

ÆTIOLOGY

Causal organism.—*Leishmania donovani* is a protozoon of the family Trypanosomidæ, other members of the genus are *L. tropica*, the causal organism of cutaneous leishmaniasis, or oriental sore, and *L. brasiliensis*, the causal organism of South American leishmaniasis, or espundia. The parasite of the infantile type of kala-azar has been named *L. infantum*, but there is little evidence that this organism differs in any way from *L. donovani*. The parasite that causes leishmania infection in dogs has been called *L. canis*, but there is evidence that, in some instances, at least, this also is identical with *L. donovani*.

Morphology and Life-cycle of *Leishmania donovani*

Two forms of the parasite are known: the non-flagellate or 'round' form, the Leishman-Donovan body, in which form it occurs in the body of its mammalian host, and the flagellate form, in which it occurs in its arthropod host (*vide infra*). The development from the round form to the flagellate form will also take place in culture medium.

Non-flagellate form.—The non-flagellate form is an oval or round body with an average diameter of about 2μ , the breadth in the oval form being about three-quarters of the length. It consists of cytoplasm containing a nucleus which is more or less round and a little less than 1μ in diameter, a parabasal body from which springs a rhizoplast, and a vacuole.

The Leishman-Donovan body is found in the endothelial cells and large wandering macrophages in all parts of the host's body. The parasites are therefore found in the tissues and organs richest in reticulo-endothelial cells, *i.e.* in the spleen, liver, bone marrow, lymphatic glands and in the submucosa in all parts of the respiratory and intestinal tracts. In the blood they are also seen in the polymorphonuclear leucocytes, in which they are apparently undergoing phagocytosis, and in the large mononuclear cells in which there is evidence of rapid multiplication; in smears made from spleen material extra-cellular parasites are often seen, but there is every reason to believe that these have come from large endothelial cells which have ruptured during the process of making the smear. The parasites are seldom found in the parenchymatous cells of the organs. In China and in the Sudan they are said to be found in large numbers in the lymphatic glands, but in India it has been difficult to demonstrate them in this site.

Viable parasites in this form have been demonstrated in the fæces (Mackie, 1914), in the urine (Shortt, 1923), and in nasal secretion (Forkner and Zia, 1934); their presence in these excreta and secretions must be looked upon as accidental, depending as it does on the separation of small pieces of mucous membrane with its submucosa, which is not the usual result of leishmania infection but is due to some coincident secondary infection.

Whilst the immediate viability of these parasites in the stools and nasal secretions has been demonstrated by animal experiment, there is no reason to believe that, outside the body, they remain viable for more than a matter of hours. A pure growth of leishmania has been obtained from

sterile urine, but in the presence of other organisms the leishmaniae are rapidly killed.

Flagellate stage.—The flagellate form shows several morphological variations, but, generally speaking, it is fusiform organism with a flagellum; the length of the body is 5μ to 15μ , the breadth 0.5μ to 2.0μ , and the length of the flagellum 10μ to 15μ . The body of the flagellate consists of cytoplasm, a centrally situated nucleus, a parabasal body situated about midway between the nucleus and the anterior end of the body of the parasite, a rhizoplast and flagellum springing from the parabasal body, and a vacuole lying between the parabasal body and the anterior end of the body of the parasite (see figure 29 and plate II).

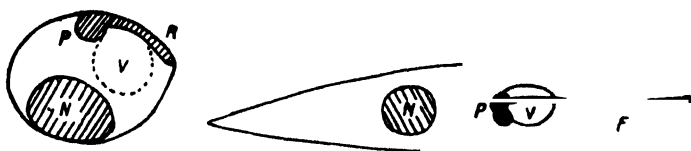


Figure 29 : Structure of Leishmania, in the 'round' and flagellate stages.

N = nucleus.	V = vacuole.
P = parabasal.	F = flagellum.
R = rhizoplast.	

Culture.—A number of different media have been used for the cultivation of leishmania, but by far the most satisfactory is NNN (Nicolle, Novy and MacNeil) medium. This is a simple saline agar preparation to which about one-third fresh rabbit's blood is added while the agar is cooling but is still in the fluid state. The blood and agar are then mixed by rotating the tube between the palms, and sloped. The hydrogen-ion concentration need not be adjusted as the blood is an efficient buffer; the pH is usually about 7.0, but good growth will take place between pH 4.7 and 8.3; actually the optimum appears to be somewhere about 6.0. The morbid material containing the leishmaniae is placed in the condensation fluid; flagellates appear within a day or two, but much longer (10 to 30 days) is usually required for the identification of a scanty infection. The optimum temperature is about $28^{\circ}\text{C}.$, but a good growth will occur at $22^{\circ}\text{C}.$

Survival and pathogenicity.—The flagellate form is a very delicate form and contamination with bacteria will rapidly kill a culture. The flagellate will not survive in water or soil, but survives in sterile milk for a few days. When injected subcutaneously it rapidly rounds up and loses its flagellum.

It has been shown that in susceptible animals, Chinese and Syrian hamsters, *Cricetulus griseus* and *Cricetus auratus*, infection can be caused by the introduction of either the round or the flagellate forms by the peritoneal, the subcutaneous, the percutaneous, the oral and the conjunctival routes; except that the flagellate form will not infect by the conjunctival route, it appears to be the more infective stage (Napier *et al.*, 1933). In man, infection is not easily conveyed by the subcutaneous route (*vide infra*).

Transmission

Historical.—Since the discovery of the parasite, forty years ago, many investigations have been undertaken to discover how kala-azar is transmitted from one person to another. Innumerable hypotheses have been propounded and

have in turn proved unsatisfactory; for some years the hypothesis that it is transmitted by certain species of sand-fly, e.g. *Phlebotomus argentipes*, has received general acceptance; and recent investigations have proved that *P. argentipes* is capable of transmitting the infection from man to man by its bite.

The finding of parasites in various excreta and secretions has naturally led to the suggestion that direct transmission from man to man might occur in nature, but the epidemiology of the disease negates these suggestions. To take one point only, the strict geographical limitations of the disease seem to indicate some more complicated biological process which demands special meteorological and physiographical conditions. This led to the suggestion that leishmaniae were the natural parasite of some insect and that man was an intermediate host; the bed-bug, the flea, and several flying blood-sucking insects were considered and in turn discarded after experimental work had yielded negative results.

The workers at the Calcutta School of Tropical Medicine were impressed by the fact that, of the various blood-sucking insects under suspicion, the local distribution in Calcutta of the sand-fly, *Phlebotomus argentipes*, corresponded most closely with the distribution of kala-azar and that the geographical distribution of this particular species of sand-fly in India, as far as it was known, again appeared to correspond with that of kala-azar. They showed that under the conditions in which kala-azar was most prevalent, this sand-fly was a persistent human-blood feeder, and in a series of experiments with laboratory-bred *P. argentipes* they showed that, when these flies were fed on a kala-azar patient, a heavy flagellate infection developed in about 25 per cent of the flies so fed (Knowles, Napier, and Smith, 1924); they also found that this same degree of development did not occur in other species. Other workers confirmed this observation, and Shortt, Barraud, and Craighead (1926) showed that the infection passed forwards in the sand-fly, eventually infecting the buccal cavity.

Later experiments have shown that these sand-flies become infected after feeding on persons who have had kala-azar and have recovered from the visceral infection but are suffering from that interesting sequel of the infection, post-kala-azar dermal leishmaniasis (see p. 149), even in cases in which the skin lesions are so ill developed as to be scarcely perceptible (Napier *et al.*, 1933).

Isolated transmissions of the infection to Chinese hamsters, *Cricetulus griseus*, by means of the bite of the sand-fly were effected (Shortt *et al.*, 1931, and Napier *et al.*, 1933), and the matter was left at this stage for some years. More recently, Smith *et al.* (1941) have demonstrated that the survival and progress of the infection in the sand-fly depend largely on whether it takes a second blood meal or subsists on fruit or plant juices. In the latter case, a large percentage of the infected flies develop a massive infection of leishmania which blocks the pharynx and buccal cavity (*vide infra*); when these 'blocked' flies are fed on a susceptible animal, infection almost invariably takes place.

Finally, Swaminath, Shortt and Anderson (1942), by feeding flies according to the technique devised by Smith, have transmitted the disease to five out of six human volunteers who were natives of, and lived throughout the period of the experiment in, a non-endemic area.

In China, the sand-flies associated with kala-azar transmission are *P. major* and *P. major* var. *chinensis*; one or other is prevalent in all the endemic areas of the disease in that country and they have been shown to be efficient carriers (Young and Hertig, 1926). In Italy and the Mediterranean area generally, both *P. major* and *P. perniciosus*, especially the latter, are thought to be transmitters; one or other is prevalent in all the endemic areas, and Adler and Theodor (1931) have shown that the latter is an efficient carrier. In the Sudan, there are thirteen species of sand-fly, six of which bite man (Kirk and Lewis, 1940), but a sand-fly of the *P. major* group, *P. langeroni* var. *orientalis*, is believed to be the transmitter.

The future.—It seems quite possible that certain plants or fruit juices on which the sand-flies feed may favour the development of the parasite in the sand-flies more than do others, and the writer believes that future investigation along these lines may lead to the explanation of some of the remaining anomalies regarding the distribution and incidence of kala-azar.

The development of the parasite in the sand-fly, and the mechanism of transmission.—The parasite is taken into the mid-gut of the sand-fly with its blood meal; the round form becomes a flagellate form, and active

division occurs; by the third day the infection has reached the proventriculus, and by the fourth there is a massive infection of the mid-gut, the lumen being blocked by a solid plug of flagellates; by the fifth day parasites have passed through the œsophageal opening into the pharynx; and as early as the seventh day parasites have been found in the buccal cavity and have been seen lying distally to the opening of the salivary ducts. In a sand-fly that has received no subsequent blood meal but has subsisted on suitable fruit or plant juices, the pharynx will often become completely blocked.

When an infected sand-fly feeds on man, before he can take any blood, this solid block of flagellates has to be ejected, and it will naturally be injected into the wound made by the fly's proboscis. There is little local reaction to this inoculum of flagellates; some flagellates will escape into the blood stream where they will probably be destroyed, but others will be taken up by the local reticulo-endothelial tissues and undergo slow multiplication, parasitized cells will enter the circulation, they will be carried to the viscera, *e.g.* the spleen and liver, and a general infection will follow, or they may remain in this local depot until some general mobilization of macrophages takes place, as in typhoid or malaria (*vide infra*), when the leishmaniæ will be distributed to other parts of the body and again a generalized infection will occur.

The sand-fly vectors.—The three most important species are *Phlebotomus argentipes* Ann. & Brun. in India, *P. major* var. *chinensis* Newst. in China, and *P. perniciosus* Newst. in the Mediterranean area. They are all very similar in their habits.

Phlebotomus argentipes.—This is a dark brown medium-sized sand-fly, 2.3 to 2.8 mm. long; on the thorax the dorsum is black and the sides light yellow; the wings are rather broader than those of most species, and the tarsi are white. According to Sinton this species is not found outside India. It has a widespread distribution in India, but is most prevalent in Bengal and Assam, where it can be found at any time of the year, but is most prevalent during and immediately after the monsoon (*see figure 25, plate I*).

Phlebotomus major var. *chinensis*.—The colour is variable, dull greyish to bright golden yellow; the abdominal hairs are more or less erect dorsally and are a uniform golden grey with very strong silvery lights; the disc of the wings has a bluish iridescence; the eyes are black, and the legs are sometimes darker than the abdomen which is clothed with long recumbent hairs and has tufts of longer upright ones on the dorsal surface. This species is closely allied to *P. argentipes* from which it is however easily distinguished.

Phlebotomus perniciosus.—The thorax is with or without dull red-brown spots, which when present are arranged in a triangle; there is occasionally a similar spot on the vertex of the head; the eyes are black; the thorax and coxæ are pale, translucent and ochreous; the abdomen is similar but sometimes a pale smoky grey; the hairs are pallid; the wings are faintly iridescent in a strong light with a distinct metallic lustre; the abdomen is densely hairy, the largest hairs arising from the apical margin of the segments, but no distinct tufts are found as in *P.*

Sand-fly prevalence.—In Bengal there is a small rise in the sand-fly incidence curve in March in the period between the cool months and the hot dry months of April and May. The sand-flies are found in the largest numbers in cattle-sheds well protected from wind currents. They are also found in the ground-floor rooms of houses, when these are damp and ill ventilated and have a broken or unpaved floor, and especially in rooms with a window opening on to a courtyard where ducks, chickens, or goats are kept. In the rural areas they can be found in almost any hut, but they prefer those with thick mud walls, as in the cracks of these walls, which continually draw up moisture from the ground, they can find comparatively cool humid conditions at almost any time of the year.

These sand-flies breed in any earth that contains an admixture of nitrogenous matter; the larvæ are found in the corners of broken floors and in rat-holes in houses, in chicken runs, under the eaves of houses, under shrubs and trees which provide some protection from the sun and rain, and on the sloping banks of 'tanks' (reservoirs from which the villagers of Bengal obtain their water-supply).

Relation to live-stock.—They seldom breed far from their food-supply, and when the choice is between bovine and human blood they choose the former; on the other hand, they seldom feed on other domestic animals or birds. This observation is based on the examination and identification of the blood meals of many sand-flies of this species by the precipitin method (Lloyd and Napier, 1930). The deduction is therefore that cows attract sand-flies to the vicinity but at the same time withdraw the flies' attention from human hosts and are therefore a mixed blessing; on the other hand, other animals attract sand-flies by providing a suitable environment for their breeding but do not withdraw their attention and are therefore wholly noxious. This fits in with our observations on the distribution of kala-azar in towns and mixed villages; the inevitable cow in the Hindu homestead seems to provide some degree of protection to the community.

In the laboratory it has been found that these sand-flies must be bred and kept at a constant temperature of 80° to 82°F. with almost complete saturation of the atmosphere throughout the twenty-four hours, if they are to survive sufficiently long for the flagellate infection to develop fully; kept at this even temperature they will survive for three weeks or even longer. The wet-bulb temperature keeps within these narrow limits during about three months of the year in Bengal and Assam but does not in other provinces; this may account for both the geographical distribution and the seasonal incidence of kala-azar in India.

Correlation of sand-flies and kala-azar.—So far as India is concerned, every epidemiological observation fits in with the sand-fly hypothesis of transmission. Further, this sand-fly has actually been found in large numbers in every locality where kala-azar occurs; it is a persistent human-blood feeder; a large percentage of the flies that feed on an infected person acquire the infection; infected flies have been found repeatedly in nature; this is not true of other sand-flies which are more prevalent in the non-endemic areas, nor of insects of any other genus so far experimented with; in this fly an anterior development of the flagellate infection occurs and is unlikely to be purposeless (in natural flagellate infections which pass from insect to insect the development is usually posterior); and it has been shown experimentally that the fly is capable of transmitting the infection to man and other mammalian hosts by its bite (*see p. 144*). All these facts make it almost certain that this insect is the most important agent in the natural transmission of the disease from man to man in most localities, although it may not be the only agent.

Sources of infection.—It is believed that in India man is the sole source of infection of the transmitting sand-fly; naturally, during an attack of kala-azar when the parasites are usually present in the peripheral blood, he is the most prolific source of infection, but it has been shown that the post-kala-azar dermal lesions will also provide the flagellate infection. Further, it has been shown (Napier *et al.*, 1933) that a patient treated and cured (of the visceral infection) may still be a source of infection to a sand-fly. In such a case the blood culture is negative, so that infection must take place from the parasites that are lying dormant in the skin—the

causes of the later dermal lesions. It is thus easy to understand how infection, once established in a locality, remains endemic.

In the Mediterranean, as canine infection is widespread in these areas and corresponds seasonally to the human infection, it is suggested that dogs may act as carriers; there are, however, areas where the canine infection is common and human kala-azar does not occur. In China also, dogs have been repeatedly found infected in kala-azar endemic areas, but in India, on the other hand, the only canine infections reported have been in northern India where kala-azar does not occur. A natural infection of a bullock has been reported from Assam.

IMMUNOLOGY

Antigenic properties.—Noguchi demonstrated that there were differences in the antigenic structure between *L. donovani*, *L. tropica* and *L. brasiliensis*, but that *L. infantum* was antigenically identical with *L. donovani*. There are strains of *L. canis* (of the dog) that are closely related to *L. donovani* and others that are related to *L. tropica*.

The serum of the patient contains no demonstrable agglutinins. A complement fixation test with a flagellate emulsion as antigen was devised by Hindle, Hou, and Patton (1926).

Immunity.—There is evidence of some natural immunity to infection. It has been shown that healthy adult man is not always susceptible. Numerous attempts to infect man by the injection of infected material have failed, and accidental inoculations have not produced the diseases; these include four deliberate (in leper volunteers) and two accidental self-inoculations by the writer, in which no infections occurred, and five inoculations by Adler (1940) in inoperable carcinoma, in which one sub-clinical infection followed. This immunity is subject to the influence of many factors which determine infection (*vide infra*). When the disease has been cured, the patient apparently enjoys almost complete protection from a second visceral infection. This also applies in the case of the experimentally infected hamster; treated hamsters cured of a *L. donovani* infection are immune to infection with *L. canis*. There is however no cross immunity against other leishmanial infections, *e.g.* *L. tropica* which causes oriental sore.

There is no evidence that immunity can be induced by vaccination with the specific organism.

Secondary factors determining infection.—Many observations make it seem probable that some secondary factor determines the onset of the disease in a person inoculated with the parasite. It has been pointed out that the worst outbreaks in Assam were associated with conditions of economic distress or some epidemic outbreak such as the malaria epidemic in the seventies, which according to Rogers (1908) determined the original Assam epidemic, and the influenza epidemic of 1917, which preceded the last extension in this province.

On the other hand, there is little reason to suppose that general lowering of resistance is an essential preliminary to kala-azar infection, as weak and debilitated people are not usually picked out, but the writer has suggested that possibly certain specific infections might prepare the way for a general visceral invasion of the parasite in a person in whom it had been lying dormant for some time (the incubation period varies from a few weeks to a year or more), and we have produced epidemiological, serological, and cytological evidence suggesting that malaria and

enteric were two such infections; part of the evidence for the inclusion of the latter disease was that in Calcutta a large percentage of the patients diagnosed serologically or bacteriologically as enteric fever and coming from parts of the city where kala-azar was endemic subsequently returned to hospital with kala-azar.

PATHOLOGY

Morbid anatomy and histopathology.—Parasites are found in all parts of the body, particularly in tissues rich in cells of the reticulo-endothelial system, and the specific reaction of the body to invasion appears to be a multiplication and mobilization of the macrophages, the cells of this system. There is evidence that macrophage proliferation actually precedes parasitization, as often the cells in the centre of an island of histiocytic tissue will not be parasitized, whereas those at the periphery are heavily so. Nearly all the histological changes observed in the different organs are due to the proliferation of reticulo-endothelial tissue. Later, fibrotic changes may occur in some of the organs, *e.g.* liver and spleen, but these usually appear very late, and are not constant.

The **spleen** is almost always enlarged; it may be immense, weighing as much as ten pounds in an adult. The capsule is usually thickened, and occasionally at the site of recent perisplenitis there is considerable thickening. Its consistence is variable, but in most cases it is soft and pulpy, the surface bulging on section of the capsule. In the more chronic cases it is firm, retaining its shape on removal from the body but it is usually very friable and is seldom hard and fibrous like the chronic malarial spleen. The cut surface has a uniform dark-red appearance; if the knife is drawn across the cut surface of the soft type of spleen, quantities of pulp will be scraped off, and the surface will be felt to be quite smooth. There may be infarcts.

Microscopically, there is infiltration by masses of heavily parasitized macrophages; these encroach on the lymphatic follicles (Malpighian corpuscles), which eventually disappear almost completely. There is considerable enlargement of the vascular spaces. The large parasitized macrophages appear to dominate the whole picture.

The **liver** is usually enlarged. It is firm, retaining its shape well on removal from the body. It is friable, but not so friable as the spleen. The capsule is thickened in places, and the liver on section shows the greasy appearance associated with fatty degeneration. It also shows the nutmeg appearance of the chronically congested liver. The cells affected are the Küpffer's stellate cells, which are enlarged and parasitized so much that they may be wrongly identified as the parenchyma cells, which some writers have reported as being invaded in the later stages of the infection. The proliferation of these cells is most marked in the portal zone, and in some cases masses of parasitized reticulo-endothelial cells will be seen in the portal spaces. The reticulo-endothelial tissue invades the lobules and separates the liver cells. In the central zone the capillaries are dilated, and both the reticulo-endothelial and the liver cells may be atrophied. There is usually some fatty change in the parenchyma cells. Later, this increased reticulo-endothelial tissue is partially superseded by fibrous tissue, producing the interlobular cirrhosis that occurs in the later stages of the disease.

There is usually evidence of increased activity in the **bone marrow**, red marrow taking the place of the fat. Microscopically, there is a considerable reduction in the hæmopoietic tissue, which is largely displaced by

proliferating and parasitized macrophages; these may occupy almost the whole marrow space, but there are usually a few areas of hæmopoietic activity.

In other organs and tissues the changes are inconstant, and the reports of observers in different countries vary.

Although workers in China and the Sudan have reported the frequent involvement of the **lymphatic glands**, in India we have seldom noted any clinical enlargement or any considerable histological changes. There is sometimes proliferation of the reticulo-endothelial cells in the neighbourhood of the vessels; in extreme cases these cells, many of which contain parasites, invade the lymph follicles, displace the lymphatic tissue, and disorganize the whole structure of the lymph node.

The changes in the **intestinal tract** which have been reported from time to time are not constant and are certainly not specific. Proliferation and parasitization of the reticulo-endothelial cells in the submucosa have been described by various workers, especially those in China, and appear to be fairly constantly noted in the infected hamster. In the absence of secondary ulceration and post-mortem denudation, the epithelium is always intact and is not parasitized; it is therefore only by means of this secondary ulceration that parasites can escape into the intestine. De (1934) in a series of twenty-six necropsies in Calcutta failed to find this involvement of the submucosa, although he examined sections from all parts of the intestinal tract.

The histopathological findings in the **skin** are somewhat anomalous. Workers in China have demonstrated leishmaniæ in the skin of a large percentage of visceral infections, *i.e.* kala-azar, whereas we in India have failed to do so. On the other hand, the occurrence of dermal lesions (*vide infra*) as a sequel to kala-azar is common in India but is rarely reported in China. It is obvious that in the Indian cases of kala-azar too the parasites must be present in the skin but in such small numbers that it is not possible to demonstrate them.

Changes in the **adrenal cortex** due to invasion of the zona fasciculata and zona glomerulosa by parasitized macrophages are commonly but not constantly observed. Parasitized macrophages have been comparatively rarely found in the kidney, heart, testes, and thyroid.

Post-kala-azar dermal leishmaniasis.—In the early hypo-pigmented lesion of post-kala-azar dermal leishmaniasis the epidermis has undergone very little change, but there is some decrease in the pigment in the cells of the basal layer. The sub-papillary layer is œdematous, and the vessels are large and dilated, the latter change being very marked in cases with erythematous lesions. There is some infiltration by macrophages in the deeper layers around the sub-papillary plexus. Parasites are scarce in these early lesions, but can be demonstrated by cultural methods, and sand-flies allowed to feed on these areas become infected. As blood cultures are usually negative at this stage, the sand-flies must obtain the parasites from the local tissues.

In the nodular lesions the epidermis is thinned down to a few layers of cells, and the papillæ are flattened out. Below, in the reticular layer, there is much proliferation of the macrophages, which form into large masses of cells, many of which are parasitized. The xanthoma type shows proliferation around the deeper capillary plexuses and, later, constriction and dilatation of the venules, causing the deep orange-red colour of the **skin**.

Blood picture.—The most characteristic changes in the blood picture are the leucopenia and the decrease in granulocytes. Some degree of anæmia is always present, except possibly in the earliest stages. The red-cell count is constantly about 3,000,000 per c.mm.; in a series of forty-seven cases it was under 2,000,000 only once and over 3,500,000 only six times. The cell is usually slightly macrocytic and hyperchromic; nucleated red cells are not often found. The reticulocyte count is nearly always a little above normal, from 2 to 4 per cent. The fragility of the red cells to hypotonic and hypertonic saline solutions is decreased.

The decrease in leucocytes occurs early in the disease, and is a useful diagnostic sign. In 80 per cent of well-developed cases the count is below 4,000 per c.mm. (see figure 30).

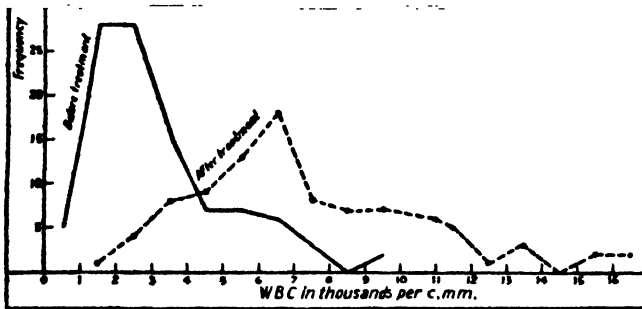


Figure 30: The leucocyte count, before and after treatment; frequency curves based on 100 cases.

Agranulocytosis has been described in China, where Zia and Forkner reported seven cases among about 70 cases of kala-azar, but we have rarely seen it in India*.

The decrease is almost entirely in the granulocytic elements, which often drop to 1,000 or even less. **Eosinophils**

are often absent and are usually not more than 1 to 2 per cent of the low total count; this diminution is less noticeable among Europeans, in whom the normal eosinophil count is about 2 per cent, but among Indians it is higher; indeed, 7 to 10 per cent cannot be considered abnormal among some Indian populations.

There is sometimes an absolute increase of large mononuclear cells, and there is always a relative increase; it has been shown by supravital staining methods that two-thirds of these cells are histiocytes. In the lymphocytes there may be a slight absolute decrease, but there is nearly always a definite relative increase. There is usually a marked shift to the left in the **Arneth count**, the mean Arneth index in thirty cases being 92.

There is nearly always a reduction in the number of **platelets**, the count being usually about 200,000 per c.mm.

The indirect van den Bergh reaction is nearly always positive; the quantitative test usually shows from 1 to 3 mg. of bilirubin per 100 c.cm.

The **erythrocyte sedimentation rate (ESR)** is very much increased, more consistently so than in any other disease (Napier and Henderson, 1931). The mean reading (Westergren) in 77 mixed cases recently examined was 68.3 ± 11.2 mm.; only in one case was the ESR below 40 mm.

Blood chemistry.—Hydrogen-ion concentration of the blood in kala-azar is slightly above the normal and the alkaline reserve is reduced. The writer (Napier, 1923) has pointed out that the true change is a reduction in the buffer action of the blood.

* Though the writer's personal experience of kala-azar during the last 20 years amounts to more than ten thousand cases, he has only had one case of complete agranulocytosis under his charge (Das Gupta and Sen Gupta, 1943).

The calcium content is reduced; it is usually below 9 milligrammes per 100 c.cm. The blood sugar is reduced, and is sometimes as low as 0.05 per cent. The lævulose tolerance is also reduced.

There is a marked reduction in the serum-albumin and a corresponding increase in the euglobulin, the pseudo-globulin remaining about normal in amount, i.e. there is an inversion in the albumin-globulin ratio. The immediate effect of treatment is to bring the ratio back towards normal (figure 31). The serum tests (see p. 164) for this disease mainly depend on this increase in the euglobulin, which is often very considerable in advanced cases.

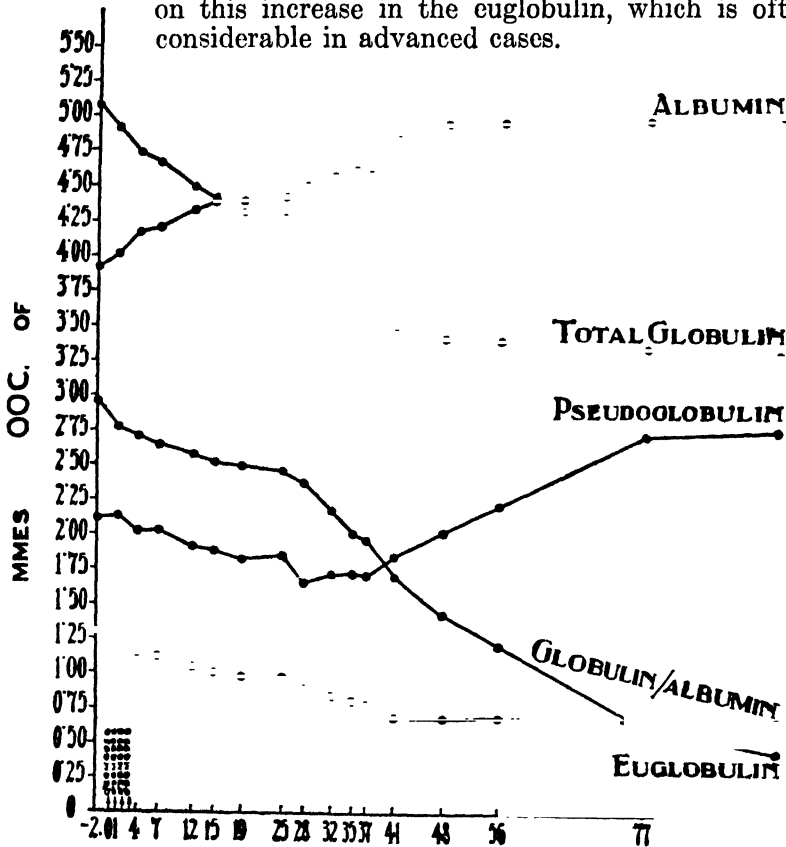


Figure 31 : The proportions of the serum proteins, before and after treatment; the latter is about normal.

The Takata-Ara test is always strongly positive. This fact, the moderately positive indirect van den Bergh reaction, the high sedimentation rate, and the disturbances in serum protein suggest considerable liver dysfunction as an early and constant feature in this disease.

Urine.—There is nearly always a trace of albumin and marked increase in urobilin. Otherwise there is no characteristic change; the urine is often concentrated and has the usual characters of a 'febrile' urine during febrile periods.

SYMPTOMATOLOGY

Incubation period.—There is very little exact information about the incubation period. Manson reported a case in which the patient had lived only ten days in the endemic area, and Muir another in which the incubation period was apparently fourteen days or less. On the other hand, the writer had a patient who had been away from any endemic area for eighteen months. In a leper inoculated with spleen-puncture material from

a kala-azar case, suggestive symptoms appeared after four months, and, in each of the five cases in which the infection was transmitted experimentally by sand-fly bites (*vide supra*), symptoms had developed within about four months of the first infected bite. The incubation period is generally considered to be from two to four months.

A case of congenital infection has been reported.

Onset.—The nature of the onset is not constant; it is sometimes acute, but in many cases it is extremely insidious. In India, the cases can be classed, as far as the onset is concerned, into three groups : the enteric-like, the malaria-like, and the insidious type.

In the **enteric-like type** the patient suffers from general malaise without any localizing symptoms, and the temperature climbs rapidly, reaching 103° or 104°F. in about a week; this is maintained for a week or so as a high continuous or a high remittent temperature, and then the temperature

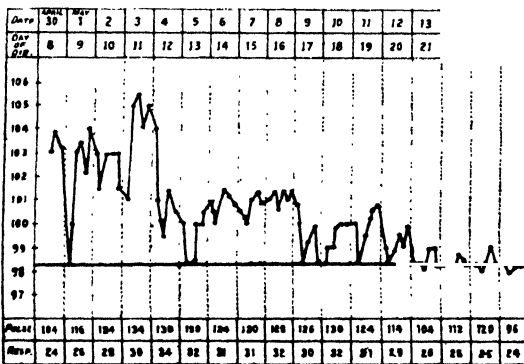


Figure 32 : Temperature at onset of kala-azar.

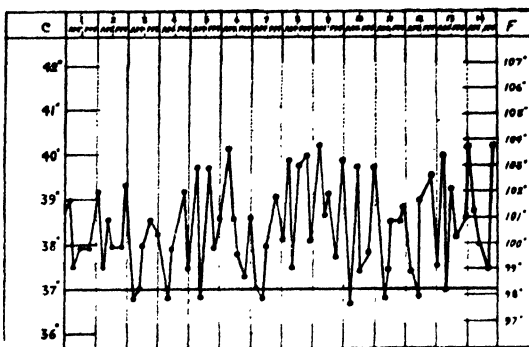


Figure 33 : Chart showing double rise of temperature in 24 hours.

gradually falls to 99°F. or even to normal. Usually abdominal symptoms are absent; the spleen is sometimes just palpable but not tender; the liver is not usually enlarged. The attack may simulate one of enteric fevers very closely, but the distinguishing features are a pulse-rate of about 120 a minute and the absence of the typical coated tongue and of the characteristic toxic drowsiness of the enteric patient.

The temperature may remain low for a week or so; then it will gradually creep up again. In this second febrile attack the temperature is more likely to be remittent or even intermittent, and the classical double rise in the twenty-four hours may appear (see figure 33). Meanwhile the spleen will have enlarged and should be definitely palpable by now. This attack may be diagnosed as an enteric fever relapse, but by the time that a third bout occurs there is little excuse for this mistake.

In the **malaria-like type**, the onset is sharper, and the fever may be accompanied by a rigor. The history in these cases is that they respond to quinine at first, but that the second attack responds less satisfactorily, and that after this, quinine does not affect the temperature at all. The splenic enlargement increases steadily and does not disappear between the attacks as it usually does in malaria.

In the **insidious type**, the patient cannot give a clear history of the time of onset of the illness but often states that for some months he has not felt well, and possibly he has had attacks of irregular fever. Eventually he

comes to hospital because of the size of his spleen or because of some complication such as dysentery or pneumonia, and it is obvious from the advanced state of the infection, indicated by the serum test, that he has been suffering for at least six months.

A modification of this is the truly **asymptomatic** type, where the patient's condition is discovered accidentally when, for example, he happens to bring another patient to hospital.

Transient infection.—In a few cases with the febrile type of onset, the infection has been transient; the parasite has been demonstrated by blood culture, but meanwhile all the symptoms have subsided, and specific treatment has not been given. The writer traced a few cases of this kind in which symptoms did not return for three or four years at least; the conclusion is that in these cases spontaneous recovery has taken place. It is possible that this occurs quite often; evidence for this suggestion is provided by typical post-kala-azar dermal leishmaniasis in patients who give a history of a transient attack of this kind, but not of definite kala-azar for which treatment was given.

Signs and symptoms of the established disease

Unless otherwise stated, the following description will apply to a patient in whom the disease has been allowed to progress unchecked for about six months; such patients present the characteristic picture of kala-azar, and in India it is at this stage that the majority seek treatment; as the disease runs a more rapid course in children, they enter this stage in three to four months.

Symptoms.—When the disease has reached a comparatively advanced stage, the patient complains of fever, progressive loss of weight, weakness increasing darkening of the skin—usually noticed by his friends—falling of the hair, palpitations and dyspnoea, intermittent attacks of diarrhoea, bleeding from the nose and from the gums, and a persistent and very irritating cough. Headaches, which would be expected with the fever, are noticeably absent in most cases, and the appetite is good and sometimes ravenous. The patient will also usually complain of progressive enlargement of the spleen; in some cases this is the first symptom; in others the enlargement is not noted for a month or two after the onset of the fever.

General appearance.—The patient may be emaciated but is often moderately well nourished; the hair is dry, lustreless, and sparse; the natural pigmentation of the skin of the forehead, of the temples, and around the mouth in dark-skinned people, is intensified and contrasts with the bloodlessness of the less pigmented part of the face; the appearance resembles that given by shading a white paper lightly with a black lead-pencil; and in some children the presence of adventitious hair is well marked; there is visible pulsation of the carotids in the neck, and the rapid pulsation of the heart is observed through the thin chest wall; the abdomen is protuberant, with the enlarged spleen and liver outlined on it; the cutaneous veins on the lower part of the chest and upper part of the abdomen stand out; the legs are thin, with tight shiny stretched skin over the shins; and the feet are possibly oedematous (see plate IV, figures 1 and 4).

Spleen.—Splenic enlargement is one of the most constant features, but cases in which there is apparently no enlargement are by no means uncommon. In a few cases the enlargement is upwards and can be demonstrated only by percussion. As a rule the spleen enlarges with the regularity and precision of a gravid uterus, reaching the level of the costal arch at the end of the first month, and being palpable one inch at the end

of the second, two inches at the end of the third, and so on; there are, however, exceptions to this general rule. There is practically no condition in which so rapid an enlargement of the spleen can take place; from being just palpable a spleen will sometimes reach the level of the umbilicus in a month; on the other hand, there are cases in which the enlargement is slow or is checked by the intervention of some inflammatory complication, such as broncho-pneumonia or cancrum oris.

The actual size of the spleen is not a very useful diagnostic point, although the regularity and comparative rapidity of the enlargement may arouse suspicion.

The peculiar soft doughy **consistence** of a kala-azar spleen, however, is highly significant; it is not common in other conditions, whereas the wood-like resistance of an old-standing chronic malarial spleen is uncommon in even a chronic case of kala-azar. 'The more chronic the disease the harder the spleen' may be taken as a general rule.

Tenderness is not common and is not complained of in more than about five per cent of cases. It is without diagnostic value, as perisplenitis is so frequent in similar diseases. Occasionally, however, a patient, either under treatment or during the course of the disease before treatment, complains of a pain in his spleen, which comes on suddenly and may last for a few days. The pain, which is at first general but soon becomes localized to one particular spot, is probably due to infarction.

Liver.—There is nearly always some degree of enlargement of the liver. An enlarged soft liver, with a thinned-out edge, overlapping a large soft spleen is very characteristic of the disease. Some tenderness is sometimes present but is in no way comparable to the tenderness associated with acute hepatitis or liver abscess. Occasionally, hepatic enlargement appears to take the place of splenic enlargement, but usually both conditions are present, and there is little evidence that this enlargement is in any way compensatory; the liver is enlarged in at least 80 per cent of all cases of kala-azar, and in those cases in which there is no splenic enlargement the liver is on the whole less often enlarged.

Jaundice is not common in the early stages of the disease, but later it may occur and is a bad prognostic sign.

Fever.—An attempt to classify the types of fever observed when once the disease is well established merely resolves itself into making the maximal number of variations by combining the words 'high' and 'low' with the words 'continuous', 'remittent', and 'intermittent', and interposing the words 'double' and 'triple' wherever suitable. There is, however, one form of fever which, when it occurs, is characteristic of the disease, i.e. the double intermittent or remittent fever; the temperature subsides towards early morning and remains low until about midday; it rises in the afternoon, subsiding again towards evening; about eight or nine o'clock at night it again rises, or the second rise may be delayed until midnight; and again it subsides towards morning. In order to demonstrate this double rise it may be necessary to take the temperature every three hours, day and night.

PLATE IV

- Fig. 1. A group of kala-azar patients attending a village treatment centre, near Calcutta. Note predominance of children and that some are well nourished.
 Fig. 2. A typical 'decayed' bungalow, with confined untidy compound in the kala-azar endemic area in Calcutta.
 Fig. 3. A typical street in the kala-azar endemic area in Calcutta; all old single-storey houses.
 Fig. 4.—A typical kala-azar subject.



Fig. 1



Fig. 2



Fig 3



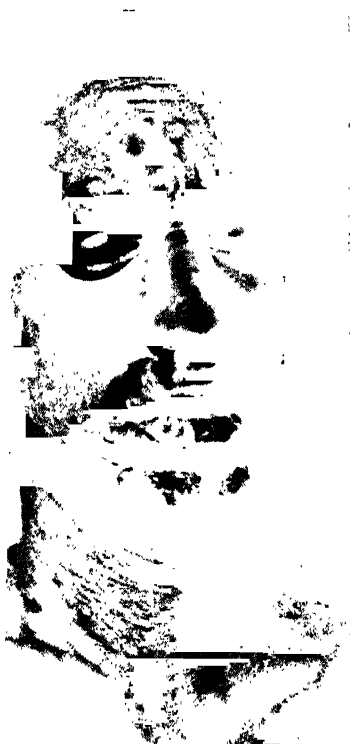
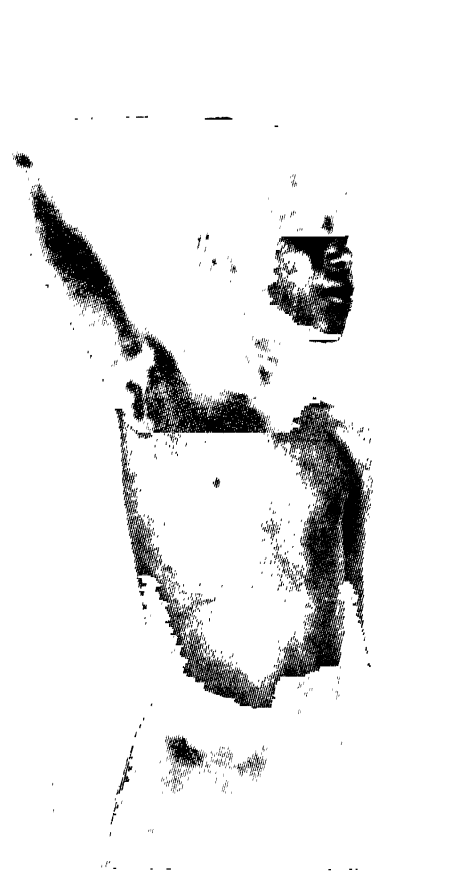


Fig. 1



Fig. 2



Some writers have exaggerated the diagnostic value of this sign, the **double diurnal rise of temperature**. It is possibly a sign that is present at some time or another during the course of the disease in most cases, and it is a sign of great diagnostic value when it is quite definitely present, but its absence is not a matter of great importance, because the chances of the condition being present at the time the patient is under observation are comparatively small. In the Carmichael Hospital for Tropical Diseases, Calcutta, where a four-hourly temperature chart is kept, a definite double diurnal rise is observed in less than 10 per cent of the kala-azar cases during their stay in hospital.

Sometimes a third diurnal rise of temperature may be recorded; this, although equally diagnostic, is not seen so often as the double rise.

Throughout the course of the untreated disease there is a tendency for periods of apyrexia to occur. During these periods the characteristic nightly rise of temperature may persist, but may not be recorded unless the temperature is taken at midnight. The nightly rise is also the last to disappear when the patient is recovering under treatment.

Some cases are truly **apyrexial**, at least from the time that they come under observation in hospital, even a two-hourly temperature chart failing to show any rise above normal over a period of weeks.

There is another characteristic point about the fever; the patient with a temperature of 102°F. may be doing his work in the ordinary way and be quite unaware that he has fever. A child will be seen playing cheerfully in the ward with a beaming smile on his face and a temperature of 104°F. in his rectum.

Cardio-vascular system.—The **blood pressure** is usually low, the systolic pressure often being below 100 mm. Hg. The very prominent pulsation of the carotids in the neck, one of the most useful clinical signs, is probably also due to this. 'Hæmic' cardiac murmurs are common.

The **heart** carries a very heavy burden of toxic effects. A certain amount of dilatation is the rule, and in a few cases hypertrophy of the heart has also been noted. Even in the earliest stages of the disease the rapidity of the **pulse rate** constitutes a valuable diagnostic sign.

Œdema of the extremities is comparatively common; it was found in 16 per cent of the Calcutta cases at the time of examination, but a very much greater number gave a history of swelling of the feet at some time.

Clinically obvious **ascites** is not common, being found in less than 3 per cent of the Calcutta cases; in advanced cases, when it is probably associated with cirrhotic changes in the liver, it occurs and is a bad prognostic sign.

PLATE V

- Fig. 1. A long-standing (five years) case of post-kala-azar dermal leishmaniasis, with involvement of both corneæ: the patient was almost blind.
- Fig. 2. The same patient as in figure 1, a little over a year later after treatment: sight in right eye almost normal.
- Fig. 3. An acute case of dermal leishmaniasis; the lesions developed to their present state in a few months, being tense, pinkish, and shiny.
- Fig. 4. Post-kala-azar dermal leishmaniasis, hypo-pigmented form. The whole skin area is involved except patches on the neck and in the axillæ and a band about 3 inches wide around the waist, where the *dhoti* is tied. In these areas the normal colour of skin is seen. The patient had kala-azar about three years before this photograph was taken.

Bleeding from the gums and epistaxis generally occur. Purpuric spots are not very uncommon and are sometimes a terminal symptom in a case running an acute course; they are often associated with uncontrollable hæmorrhage from the gums and into the bowel, a condition suggestive of Hænoch's purpura. Retinal hæmorrhages have been observed in a few cases.

Alimentary tract.—Gingivitis, with subsequent loosening of the teeth, is common. Stomatitis, other than cancrum oris, is not very uncommon at any stage, and in the late stages cancrum oris is the most classical and most fatal complication of the disease. The last-named condition, however, is not seen so often as in the days before a satisfactory form of treatment was introduced. Like œdema of the glottis, which also was formerly far commoner than now, it is always associated with extreme leucopenia.

The appetite is nearly always good, but the digestion is usually less satisfactory, with the result that intestinal disturbances may result from indiscretions in diet. Fractional gastric analyses show that there is little departure from the normal in the gastric acidity.

Diarrhœa and dysentery are such common complications that it has been suggested that there is a specific leishmanial dysentery; there is no support for this suggestion. Bowel disturbances are comparatively rare in a well-regulated hospital, and respiratory diseases are far more common complications in these circumstances; in the country districts the reverse is usually the case. A terminal dysentery sometimes occurs.

Respiratory system.—The respiratory system is peculiarly prone to inflammatory processes. At all stages of the disease an irritating cough is usually present without any considerable physical signs in the lungs to account for it. In a few cases this is the most distressing symptom of the disease, seriously interfering with the patient's rest at night. It has been suggested that this is due to irritation of the vagus from pressure caused by the enlarged spleen. In the later stages, some congestion of the bases of the lungs is common. Broncho-pneumonia is a very common complication.

The **nervous system** seems peculiarly free from attack by the parasites or their toxins. The mental condition is always quite clear, even in the final stages, and delirium is less common during pyrexial attacks in this disease than in any other, a point of diagnostic value.

Herpes zoster occurs sometimes during the course of the disease in a patient who is not under treatment, but it is much more often seen in a patient receiving antimony injections.

Skin and subcutaneous tissues.—Certain very prominent changes, probably of a trophic nature, take place in the skin of a kala-azar patient.

(i) The whole skin surface becomes dry, rough, and harsh. The hair falls out and becomes very thin; sometimes children become almost bald. Skin eruptions are common, and all sores that form are slow to heal. The parasites can sometimes be found in the granulation tissue, but their presence here is probably due not to any special local deposition but to their presence in the general circulation. Acarus infections and septic folliculitis are very common, but are probably due rather to the habits of the patient than to any special liability of the tissues to attack by these organisms. Among some peoples in India it is the custom never to allow a patient with fever to have a bath.

(ii) The characteristic blackening of the skin, from which the disease derives its name, is possibly to a certain extent due to increased activity of the melanoblasts, as there is other evidence of hypo-adrenia, but it is also probably an intensification of the natural pigmentation due to the dryness of the skin. It is most evident over the forehead and temples and occasionally around the mouth. The blackening is intensified by contrast with the anæmic pallor of the rest of the face. This pseudo pigmentation is not seen in Europeans but is very marked in dark-skinned Anglo-Indians.

The skin over the tibiæ is stretched and glossy, and this condition is usually associated with pitting over the tibial periosteum.

Urinary and reproductive systems.—Some symptoms occurring during the course of the disease suggest renal inefficiency, *i.e.* puffiness of the face, swelling of the legs, and some ascites; these are sometimes associated with a decreased output of urine. It is probable that the œdema is due to vasomotor disturbances, as the urine seldom provides evidence of any serious disturbance of renal function or to disturbance of the albumin-globulin ratio.

In women, amenorrhœa is often an early symptom and is almost invariable in a well-established case. Although conception is probably prevented in the later stages of the disease when amenorrhœa is established, the writer has seen cases in which conception occurred early in the disease; an uncomplicated pregnancy was continued to full term and was ended by the birth of a comparatively healthy child.

An instance in which the disease was apparently transmitted *in utero* came under the writer's notice some years ago. On the other hand, Muir reported the case of a pregnant woman who died of kala-azar; a necropsy was performed, and no trace of leishmania was found in the foetus.

Variations in the clinical picture in different countries

The above description applies to the clinical picture as it is seen in different places in India, and it applies generally to the disease as it is seen elsewhere, but in some countries the severe form of the disease is more common. In the Sudan, Stephenson (1940) has described an epidemic in which there was an 84 per cent mortality despite treatment. High fever, intractable diarrhœa, and hæmorrhages are the rule, and fatal complications, such as cancrum oris and pneumonia, are common.

Kirk and Sati (1940) have described a punctate rash which usually appears during the course of antimony treatment, but sometimes independently of any treatment. Similar rashes have from time to time been observed in Indian kala-azar, but their specificity was questioned. They are quite distinct from the post-kala-azar dermal lesions. In the Sudan, ulcers also appear to be a common complication and Kirk and Macdonald (1940) have described neurites and footdrop; neither has been observed by the writer, in India.

SEQUELÆ

Other than post-kala-azar dermal leishmaniasis, there are few sequelæ of importance, and there is every reason to believe that after satisfactory treatment most patients recover completely and regain their original state of health. A condition of splenomegaly, anæmia, and leucopenia appears to have occurred about two years after an attack of kala-azar in a few of our cases, but this syndrome is fairly common in Bengal, and the proof that it occurs only in kala-azar cases is lacking; it has not been reported from elsewhere.

Post-kala-azar dermal leishmaniasis.—Besides the biological interest that is aroused by this example of a change in the tropism of a micro-organism from a visceral to a dermal one, post-kala-azar dermal leishmaniasis is interesting from a number of points of view. When the first case was described (Brahmachari, 1922), it was looked upon as a pathological freak; it remained a rare finding for a year or two; since then apparently its incidence has steadily increased, and at the Calcutta School of Tropical Medicine notes have now been collected on over a thousand cases. Cases have been reported from Madras, very few from Assam, but, except for an isolated case here and there from China and the Sudan, none from the endemic areas outside India.

The observation that this form of dermal leishmaniasis is confined to the oldest endemic areas of kala-azar, and its apparent increase in incidence as the wave of kala-azar subsides, led to the suggestion that it was an example of host-parasite adjustment (Napier and Krishnan, 1931). That it is a sequel to the generalized visceral infection, kala-azar, there can be no possible doubt; two-thirds of the patients give a history of having had kala-azar and treatment for it, and nearly all the rest give a history of some febrile illness that might well have been kala-azar; there is a time relation between the visceral and dermal diseases, the latter making its first appearance usually about a year after the visceral attack has been completely cured; and finally, the leishmania that is always recoverable from the dermal lesions is in every way identical with *Leishmania donovani*, morphologically, in culture, in its development in the sand-fly, and in the production of lesions in experimental animals. Any suggestion that it is related to oriental sore, clinically an entirely different lesion, even in its non-ulcerating form, can be dismissed immediately; oriental sore does not occur in Bengal, and dermal leishmaniasis has never been reported from areas where oriental sore is endemic.

A few years ago we estimated that in Bengal this condition followed in 5 per cent of all cases of kala-azar; subsequent experience has suggested that this was possibly an underestimate. Sand-flies feeding on these patients with dermal lesions readily become infected with leishmania. From an epidemiological point of view, therefore, this sequel may be very important.

Clinically, the dermal lesions take many forms, but the hypo-pigmented macule, the butterfly erythema, and the nodule are the commonest forms.

The **hypo-pigmented macules** appear on any part of the body; the commonest sites are the upper trunk, arms, thighs, forearms, legs, abdomen, and neck, in that order; less common sites are the face, hands, and feet. The macules are pin-point at first and increase up to about half an inch in diameter; although the individual macules are seldom larger, they may coalesce and form patches; they usually appear in different parts of the body simultaneously and not in successive crops. The whole body may be affected, with the result that a dark-skinned Indian acquires the colour of a fair Irani. When this occurs there is usually a small area of skin somewhere in the body which has retained its original colour; Smith and Haldar (1935) pointed out that the waistline, where the *dhoti* was tied round and caused a constriction, often escaped depigmentation. On certain parts of the body, the macules gradually develop into nodules, but on the trunk, arms, and thighs they usually remain as macules. The degree of loss of pigmentation is fairly constant; it is never complete as in leucoderma but the colour is reduced as noted above (see plate V, figure 4).

The **butterfly erythema**, a typical form, occurs on the face, involving the nose, cheeks, and chin, but cases have been seen in which there was a flush over the whole body. The area involved is very photo-sensitive; in the early mornings it is sometimes unnoticeable, but by mid-day, after the patient has been in the bright light for a few hours, it becomes very prominent. Underlying the erythema there is sometimes a little depigmentation. This is again an early manifestation, coming on about a year after the kala-azar has been cured; it is usually associated with hypo-pigmented macules on other parts of the body; it usually disappears when the nodules develop, but it may persist for a year or two.

Nodules are generally a later manifestation, but they may be the first to be noticed by the patient. They usually occur on the face and are comparatively rare on other parts of the body; the nose, chin, and cheek are the commonest sites, but there may also be nodules on the lips, forehead and ears (*see* plate V) and more rarely on the mucous membranes, *e.g.* the tongue.

They usually grow at the site of a hypo-pigmented patch or in the erythematous area, but occasionally they appear in normal skin. They sometimes occur in the mucous membranes of the lips, and they have been noted on the palate; in one case the nodules on the palate had broken down and ulcerated. Ulceration is very rare, and even when a nodule is removed for diagnosis the wound heals rapidly. The nodules on the face may be very numerous and simulate leprosy very closely; one of our patients had been treated for thirty years as a leper.

Many other types of lesion have been seen and described (Napier and Das Gupta, 1934), the verrucose, papillomatous, hypertrophic, and xanthoma types.

Recently, we encountered a case (Napier, Kirwan and Sen, 1941) in which there was a nodule on the cornea in which *leishmaniæ* could be demonstrated (plate V. figures 1 and 2).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In the endemic areas, the diagnosis of a case of well-developed kala-azar does not present any difficulties. Although a diagnosis can be made with a fair amount of assurance on clinical grounds, it is unjustifiable to make one on these grounds alone, in view of the simplicity of the serum tests; these, however, are not of value in the earliest stages, when the diagnosis will have to depend on the demonstration of the parasite (*see* pp. 160–163). A strongly positive aldehyde reaction (*see* p. 164) in a patient with suggestive signs and symptoms is sufficient evidence for all practical purposes, but, for scientific purposes, especially if the data are to be used for appraising the value of different forms of treatment, the presence of the parasite should be demonstrated.

In the **early stages** of the disease (one month), most information will be obtained from the temperature chart. If the temperature assumes the typical double diurnal remittent form, strong suspicions will naturally be aroused, but this form of temperature is comparatively rare. The temperature chart shown in figure 32 is very characteristic; after a month's pyrexia there is often a period of some days' apyrexia and then a steadily mounting remittent temperature without any accompanying increase of symptoms or any physical signs, except possibly the appearance of the spleen at the level of the costal arch and a pulse rate above 100; the

clean tongue and the mental alertness of the patient will be helpful signs. At this stage the leucocyte count will usually be about 4,000 per c.mm. The serum tests will not be very helpful. The aldehyde test may be negative, but the experienced will often detect a faint cloud which should arouse suspicion in an early case, and the antimony test may be suggestive. The diagnosis can be confirmed by identifying the parasites in the peripheral blood, by blood culture, or by gland or sternum puncture, as the spleen may not be easily punctured at this stage.

In the later stages (five months), the points of diagnostic value are the history of a long-continued fever resistant to quinine, progressive enlargement of the spleen, loss of weight, epistaxis or bleeding from the gums, falling of the hair, and increasing darkness of complexion (in dark-skinned people). Additional physical signs will be the spongy consistence of the enlarged spleen, the enlargement of the liver, the pulsation of the carotids in the neck, the clean tongue, and the rapid pulse.

Leucopenia will now be established, and the leucocyte count will almost certainly be below 4,000 and possibly as low as 2,000 per c.mm.; eosinophils will be few or absent, and granulocytes will form less than 50 per cent in the differential count; and the red cells will number about 3,000,000 and will be slightly hyperchromic. The aldehyde test will now be strongly positive. If it is desirable to confirm the diagnosis, after failure to find the parasite in the peripheral blood, puncture of the lymphatic glands, sternum, or spleen is the easiest method at this stage.

It should be remembered that every sign and symptom of the disease may be absent; the writer has seen many cases that were afebrile for months at a time, if not throughout the disease, and many in which the spleen was not palpable.

Therapeutic tests.—It may be justifiable to exclude other infections, such as malaria, by giving quinine, but it is never justifiable to give a few antimony injections to exclude kala-azar.

If other conditions that require immediate action can be excluded, it is far better to await developments than to rush into a diagnosis of kala-azar. Once treatment is begun, diagnosis becomes far more difficult. Patients do not die in the early stages of the disease (in India, at least) and, although their temperatures may run very high, they do not suffer much discomfort. There is no truth in the oft-repeated statement that the prognosis is better if the treatment is undertaken early; on the contrary, the best results are obtained in cases in which there is a history of four or five months' illness, as in these cases the patient's natural resistance has had time to develop. Nevertheless, in most circumstances treatment should be undertaken immediately a definite diagnosis is made.

In special circumstances it may be justifiable to make a provisional diagnosis of kala-azar and to give a *full course* of treatment, but once the treatment has been started failure to effect an early improvement must not be allowed to discourage one. Many resistant cases of kala-azar give a history of therapeutic tests and tinkering treatment of this kind.

Diagnostic methods

Parasites in the peripheral blood.—Parasites are always present in the peripheral blood in an untreated case of kala-azar; their discovery depends on the persistence of the searcher and the methods adopted. By searching four films made with a straight 'leucocytic edge', as suggested by Wright

for the opsonic index, and stained by Leishman's or Giemsa's method, it should be possible to establish a diagnosis in 60 to 70 per cent of cases. Casual examination of an ordinary blood smear is of little value.

Blood culture should produce a positive result in 100 per cent of cases if the technique is beyond reproach, but it is a slow method, and it is unsafe to discard a culture as negative in less than one month, although a positive result may be obtained within a week. Blood is taken from a vein in an oil-sterilized syringe; 0.5 c.cm. is added to 10 c.cm. of saline, 0.85 per cent containing 2 per cent of sodium citrate; the cells are allowed to settle; the cellular deposit is then sown into NNN tubes (a rabbit's-blood agar slope with condensation fluid); these tubes are kept at 22°C., and a drop of the condensation fluid is examined at intervals in the fresh state. The flagellates will be seen as actively moving forms among the red cells. As the medium is easily contaminated it is advisable to sow into at least three tubes.

Sternum puncture.—Recent experience has shown that this is a very valuable method of diagnosis. In a recent series of 80 subsequently proven cases of kala-azar, parasites were found in the sternum puncture smear in 71, or 89 per cent; in six of nine cases in which no parasites were found, a spleen puncture was done and parasites were found in the smear in three; in the remainder a positive culture was obtained. In a sternum puncture smear, parasites are always more difficult to find than in a spleen puncture smear from the same case, and in cases in which parasites are scanty they may easily not be found in the former. Thus, though it is a valuable additional method, and one that can be employed when the spleen is not puncturable, it has not replaced spleen puncture. It is a more painful procedure, and, though probably safer, experience has still to prove this.

A culture on NNN medium can be made from the material obtained by sternum puncture, but it is difficult with the apparatus at present at our disposal to avoid contamination; satisfactory cultures will however always show leishmaniae in a case of kala-azar.

Technique of sternum puncture.—The Salah needle used for sternum puncture is shown below (figure 34). It is made of rustless steel and the bore is about the

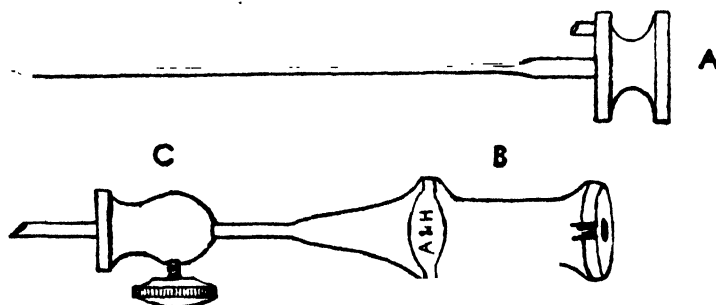


Figure 34 : Sternum-puncture needle (actual)

same as that of a lumbar-puncture needle. The guard C on the needle can be moved so as to adjust the depth of the puncture. Usually the guard has to be fixed at a distance of 1 to 1.5 cm. from the tip in order that the marrow may be reached. This distance will vary with the thickness of the skin and subcutaneous tissue of the thoracic wall; in fat individuals as much as 2 cm. may be required and in very emaciated ones less than 1 cm. It may be found advisable to readjust the guard after the needle has reached the periosteum, before it is pushed through the outer plate into the marrow cavity. The stylet A is kept in while the puncture is being made and is withdrawn after the cavity is reached.

Procedure.—The hair over the sternum, if there is any, is first clipped with a pair of scissors, shaved with a razor, and the skin finally cleaned thoroughly with alcohol. The best site for the puncture is just to one side of the middle line at the level of the second intercostal space. This area is first anesthetized by infiltration with a 2-per-cent solution of novocaine, or its substitute. Some solution is first injected into the skin with a fine needle attached to a 2-c.cm. syringe; then the needle is pushed down to the periosteum and the rest of the solution injected. About 1 c.cm. is usually sufficient in a thin individual, but more is required where the subcutaneous tissue is deeper. After an interval of 5 to 10 minutes, the actual puncture is made.

The apparatus is held with the knob of the stylet in the palm of the hand, and the needle itself between the thumb and index finger, the latter being on the guard C of the needle. Pressure is applied and the skin and subcutaneous tissues are pierced; a rotatory movement will then facilitate puncture of the outer plate of the sternum. As the external plate of the sternum is pierced and the marrow cavity is entered, there is a sensation of loss of resistance, just as is felt on entering the spinal canal during lumbar puncture. The stylet is now taken out, a dry-sterilized 2-c.cm. all-glass or Record syringe is attached to the end of the needle, and the marrow blood is aspirated. When the fluid is aspirated, the patient feels a dragging pain which is a guide as to whether the needle is in the marrow cavity or not. Only a few drops of marrow (sinusoidal) blood are removed and the syringe and the sternum-puncture needle are withdrawn; digital pressure is applied over the puncture for a minute or two and the puncture is sealed with collodion. With the needle still attached to the syringe one drop is placed into NNN medium and the rest placed on clean slides for smears to be made; these are stained with Leishman's or Giemsa's stain and examined in the usual way.

Only very rarely will one fail to obtain blood. The commonest error is to fail to allow a sufficient length of needle. In this case the guard must be adjusted slightly, the stylet replaced, and the needle pushed in a little deeper. Occasionally, the needle goes too deeply and has to be withdrawn slightly before blood will come.

Tibia puncture.—This is useful in small children, up to the age of about two years, especially as in these young children the sternum is very soft, and unaided will not usually support the needle while the stylet is removed.

The percentage of positive findings is however smaller.

The puncture is made about the middle of the shaft of the tibia with a sternum-puncture needle. More force is required as the bone is denser even than the sternum of an adult.

Spleen puncture.—The dangers of spleen puncture are much exaggerated, but nevertheless it should never be performed unnecessarily or carelessly, and the adoption of a rigid technique is advisable. In 95 per cent of cases of kala-azar the parasites will be found in large numbers in the smear (stained by Leishman's or Giemsa's method) and in every case by cultivation directly into NNN medium.

Technique of spleen puncture

Preparation of patient.—If possible the patient is given a dose of calcium lactate 30 grains on the previous night, another dose in the morning, and a third dose immediately after the operation. The patient is given no food on the morning of the operation, and is kept in bed for the day; he is allowed food one hour after the puncture.

The writer has followed this procedure whenever possible for over 20 years and he has had no disasters in over 7,000 spleen punctures; he therefore hesitates to abandon it, though he is doubtful if it is necessary, or even if the rationale is sound. In the out-patient department he has used a considerably modified procedure, reducing the calcium lactate to two doses and the resting time to one hour after the puncture, with equally good results.

Procedure.—The puncture is done with a 5-c.cm. syringe and a no. 11 needle, about 1 to 1½ inches in length. If possible a special spleen-puncture attachment should be used (Napier, 1936), but, although it facilitates the operation and must

correspondingly decrease the danger, it is not essential (figure 35). The syringe is oil-sterilized, or, if an all-glass syringe is used, it may be dry-sterilized.

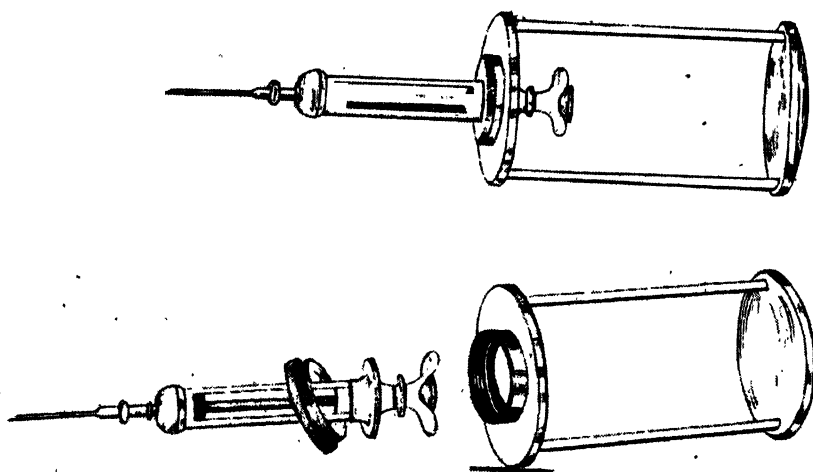


Figure 35 : Spleen-puncture fitment for syringe.

The patient lies on a flat bed, with fracture boards if necessary, without a pillow, and the operator sits on the edge of the bed on the left of the patient. The splenic area is sterilized with alcohol. The spot chosen for the puncture is half an inch below the costal margin about the centre of the parietal surface of the spleen; at this spot the skin is touched with pure phenol, which after a minute is wiped off with a spirit swab. If an ordinary syringe is used, an assistant, standing on the other side of the bed, should place his right hand below the spleen to prevent downward movement; if the special spleen-puncture attachment is used, the operator's left hand is free and he can do this himself.

The puncture is made in two movements. By the first the skin alone is punctured; this can be done at a very acute angle with the skin surface; just the tip of the needle should go through the skin. The direction of the needle is then changed, and it should be pointed in an upward and outward direction, parallel with the long axis of the spleen and at an angle of about 45° with the skin surface; the needle is then plunged into the spleen, the piston withdrawn rapidly two or three times, and the needle withdrawn. Whereas the first movement is done slowly and deliberately, the second, the puncture of the spleen, must be done rapidly, because the longer the needle remains in the spleen the greater is the danger of tearing the capsule. The contents of the syringe are ejected on to a slide and into culture medium. It is necessary to have only the smallest trace of blood in the needle, and not on any account must the withdrawal of the plunger be continued because blood cannot be seen in the syringe. Sometimes the syringe does fill rapidly with blood, but this is not a serious matter.

A binder should be put round the abdomen with a pad over the point where the puncture was made. In about 10 per cent of cases the spleen is tender for the next 24 hours, but most patients do not have any discomfort.

Liver puncture.—In the writer's practice, sternum puncture has entirely displaced liver puncture; the latter holds no advantages over the former, and has many disadvantages, but in the absence of a palpable spleen and special sternum puncture needle or a suitable improvisation, it may be indicated.

In at least 10 per cent of kala-azar cases parasites will not be found in the smears, although culture will probably give 100 per cent positive results. It is usually necessary to make the puncture between the ribs, and also to withdraw the plunger a number of times to be certain of obtaining blood, as the organ is not so vascular as the spleen. Otherwise there is little difference in the technique.

Gland puncture.—In China (Cochrane, 1912) and in the Sudan (Kirk and Sati, 1940) gland puncture is found a useful method of diagnosis; in the latter workers' experience, a diagnosis can always be made by this method, but other workers in the Sudan have been less successful. In India, we seldom find the lymphatic glands sufficiently enlarged for the puncture to be made, and when, in an emaciated patient, it is possible to grip the glands between the finger and thumb, the findings are usually negative.

Procedure.—Take a medium-sized dry-sterilized hypodermic needle (no. 11). Grip a lymphatic gland, *e.g.* an inguinal or a cervical gland, between the finger and thumb, and, after sterilizing the skin, plunge the needle into the gland and leave it for half a minute or so. Then withdraw it and force out the contained fluid on to a slide and into culture medium in the ordinary way; scanty leishmaniae will usually be found, and will grow in the NNN medium. It is usually possible to obtain enough fluid without suction, but this may assist.

Serum tests

The serum tests all depend on the increase in the euglobulin fraction (*vide supra*). Many modifications have been introduced, but the writer much prefers the aldehyde test. Chopra's antimony test has the advantage of giving a positive result earlier in the disease, but in cases with a large spleen not due to kala-azar it is liable to give a false positive; therefore, in an early case without splenic enlargement, both tests should be done; but in a well-established case with a large spleen, the aldehyde test can be relied upon.

Aldehyde (Napier) test.—This reaction is not fully developed until the third to the fifth month, and after successful treatment takes about four months to disappear, so that it is of little value as a test for cure.

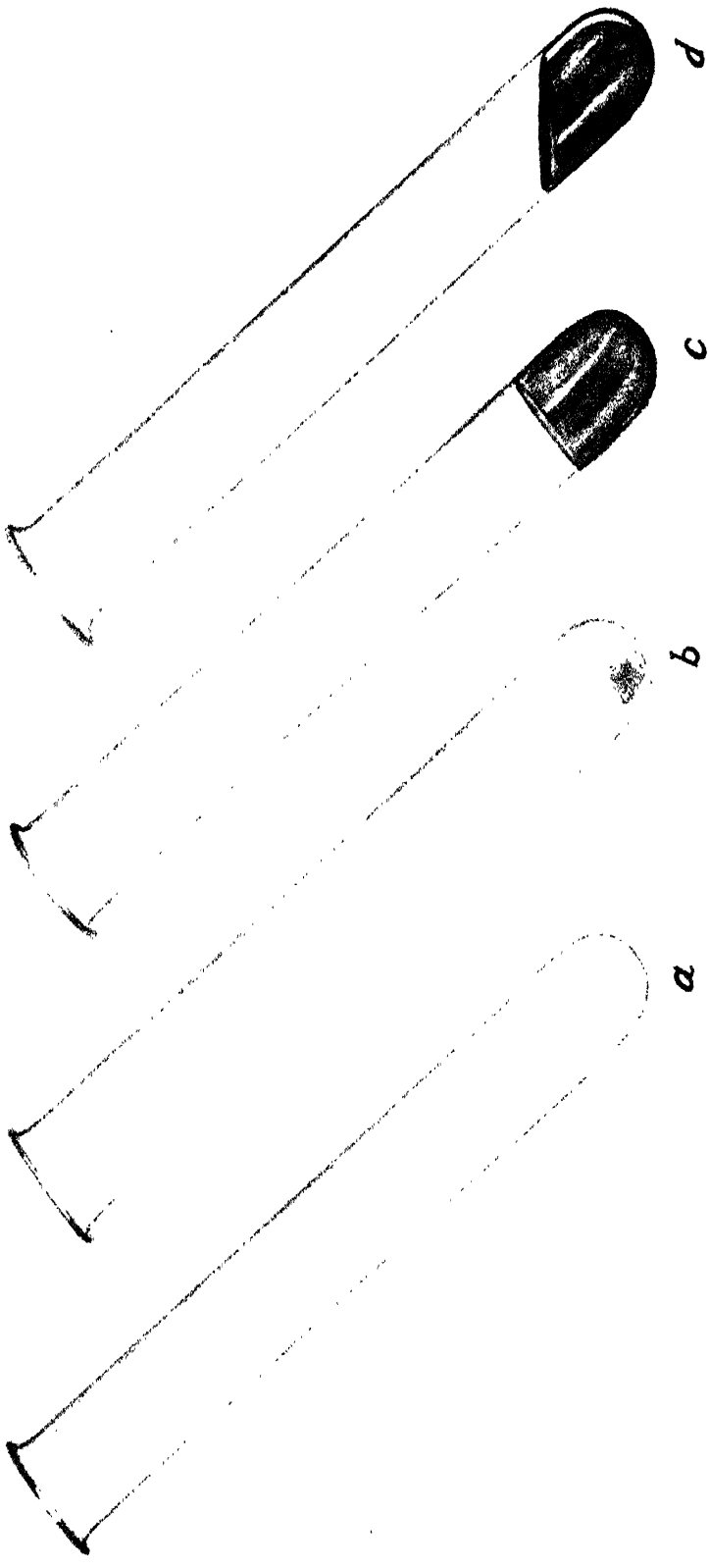
To 1 c.cm. of clear serum, one or two drops of commercial formalin are added. In a strongly positive result the serum becomes solid and completely opaque, like the white of a hard-boiled egg, within a very few minutes; if it becomes completely opaque within 24 hours the result is still considered positive. Doubtful results are solidification of the serum with various degrees of cloudiness. In a negative result the serum remains crystal-clear, although it may solidify (*see plate VI*).

Diagnostic value of test.—The test is seldom completely negative after one month from the onset of the disease, and after five months it is nearly always strongly positive. Although the margin between these two events appears to be a wide one, in actual practice in an endemic area it has been found that with this test a definite diagnosis can be made with very little risk of error in at least 70 per cent of cases that attend the out-patient department; for example, a negative diagnosis can be made in a patient with a long history of illness and a spleen below the navel, if the test gives a doubtful or negative result (as it would certainly be positive if the disease were kala-azar), but, if the same doubtful result were given in the case of a patient with a very small spleen and a short history of fever, it would be necessary to take other steps to exclude kala-azar.

A definitely positive reaction may be taken as indicating kala-azar. In Calcutta, where neither trypanosomiasis nor schistosomiasis occurs, in at least 20,000 tests, the writer has only encountered a dozen instances in which the result was positive in cases other than kala-azar.

Antimony (Chopra) test.—The serum is diluted ten times with double-distilled water and is placed in a narrow-bored test-tube; to this, 4 per cent urca-stibamine solution is added with a Wright's pipette. The tube is then rotated between the palms to mix the contents. In a strongly positive reaction there is a heavy flocculent precipitate, in a less strongly positive reaction a fine flocculent precipitate, in a doubtful reaction a distinct cloudiness, and in a negative reaction the two fluids mix without any precipitation (*see plate VII*).

There is usually a doubtful reaction at the end of the first month or even earlier and a positive one at the end of the second or third month. In cases of enlarged spleen from other causes, a positive reaction is sometimes given; therefore the test can be relied on only in cases with little splenic enlargement.



Reading the result. The final result should be read at the end of 24 hours, but with experience a very good idea of the probable result will be obtained in half an hour.

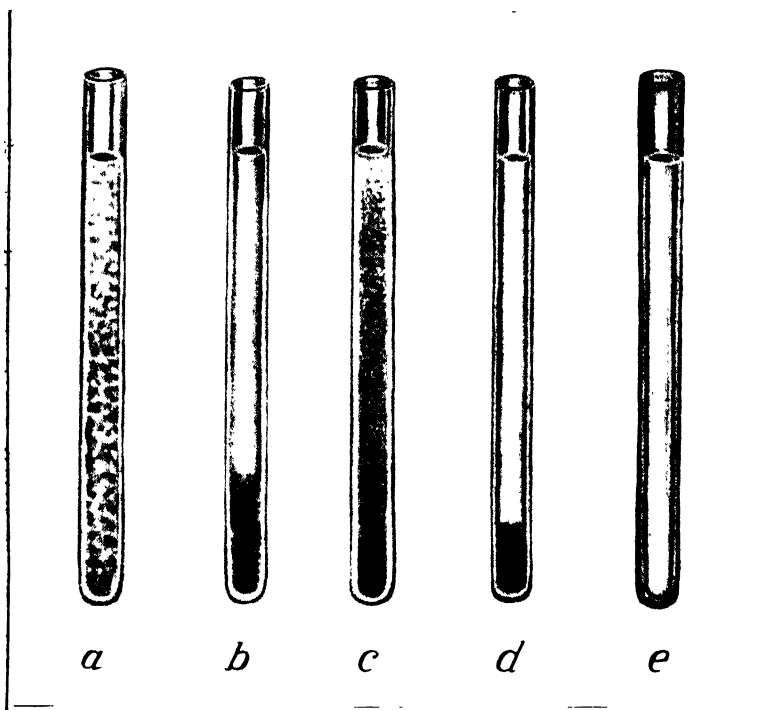
(a) *Positive.* Solid, white and completely opaque (hard-boiled egg); no light transmitted through the serum. If complete opacity is produced in 20 minutes, the result is $++$, if in two hours, $++$, and if in 24 hours, $+$.

(b) *Doubtful* ($+$). Solid, with milky appearance which looks opaque against a dark background, but shows the shape of the window when held up to the light, after 24 hours.

(c) *Doubtful* \pm . Solid, slightly milky but quite transparent, after 24 hours.

(d) *Negative* (-). Solid but crystal clear, after 24 hours.

(e) *Negative* - *inc.* Serum unchanged (fluid), after 24 hours. (For interpretation see plate VII.)



Reading the result

(*a* and *b*) *Positive*. This is indicated by a heavy flocculent precipitate forming almost immediately; this settles as a flocculent mass in the course of half an hour or so.

(*c* and *d*) *Doubtful*. This is indicated by a fine granular precipitate which settles more slowly, but forms a more compact mass at the bottom of the tube.

(*e*) *Negative*. In a negative result no precipitate occurs.

Size of spleen	Antimony test reading	Positive	Doubtful	Negative
Below the navel	Doubtful	Not kala-azar	Not kala-azar
Four inches or more below costal margin but not below the navel.	Probably kala-azar.	Doubtful	Not kala-azar
Two inches or more but less than four below costal margin.	Kala-azar*	Doubtful	Probably not kala-azar.
Palpable, but less than two inches below costal margin, or not palpable.	Kala-azar*	Doubtful	Doubtful

Interpretation of results of aldehyde test

Size of spleen	Aldehyde test reading +++, ++, or +*	(+)	±	(--)	ive
Below the navel	Kala-azar	Doubtful	Not kala-azar.	Not kala-azar.	Not kala-azar.
Four inches or more below costal margin but not below the navel.	Kala-azar	Probably kala-azar.*	Possibly kala-azar.	Probably not kala-azar.	Not kala-azar.
Two inches or more but less than four below costal margin.	Kala-azar	Kala-azar*	Possibly kala-azar.	Probably not kala-azar.	Doubtful
Palpable, but less than two inches below costal margin, or not pal-	Kala-azar	Kala-azar*	Possibly kala-azar.	Doubtful	Doubtful

Globulin-precipitation test.—In the globulin-precipitation test one part of serum is added to two parts of distilled water. In kala-azar a flocculent precipitate forms. The test has the same limitations as the above two tests and is less specific.

Other experience.—In the Sudan, the serum tests have not proved of much value, and in China the more delicate tests, which give very misleading results in India, *e.g.* the globulin-precipitation test, are sometimes preferred to the aldehyde test. A recent elaboration is a photometric test with 1 in 1,000 dilution of serum and 1 in 100 urea-stibamine solution (d'Oelsnitz, 1938).

Diagnosis of post-kala-azar dermal leishmaniasis.—The hypopigmented macules and the erythematous rash are clinically very typical, and will seldom be mistaken by those with experience of the disease; in these cases parasites can be found in the tissues, but it is difficult to demonstrate them, and there is no simple procedure which can be recommended for routine use. On the other hand, in the nodules, the parasites can be detected with ease; a nodule is seized with a fine pair of forceps and snipped off with a pair of curved scissors; smears are made by rubbing the cut surface of this nodule on a slide, which is then stained by Leishman's or Giemsa's method. Typical parasites will be seen lying in endothelial cells or free as a result of rupture of a cell.

PREVENTION

A sufficiently large number of facts regarding the epidemiology of the disease has been accumulated for us to recognize the conditions under which transmission occurs, and the first measure of prevention is to avoid these; the reader is referred back to pages 139–142.

For transmission to occur two factors are necessary, (*a*) *the source of infection* and (*b*) *the transmitting insects*, and preventive measures can be considered under these two headings.

(*a*) **The source of infection.**—There are in India, as far as we know, no animal reservoirs of infection, so that man is always the source of infection. A patient with kala-azar will be the richest source of infection, but once treatment has been started the parasites usually disappear from the peripheral blood.

The only control measure that has been undertaken on a public health scale has been a treatment campaign. Such a scheme was instituted in Assam from the year 1922 onwards. A similar scheme was put into operation in Bengal a few years later. These treatment campaigns undoubtedly had a great influence in controlling the disease in these provinces, in cutting short the epidemic in the former, and possibly in delaying the next epidemic wave which, according to previous experience, is already overdue. In Bihar, which was never such a highly endemic area, but in which no treatment campaign was undertaken, there has been a marked rise in incidence in the last year or so; no similar rise is yet (1942) apparent in the other two provinces.

In a small experimental area near Calcutta where we undertook an intensive treatment campaign about 15 years ago, there has been no recrudescence of the disease; in an area where there were 121 and 137 cases in the years 1925 and 1926, there were no cases in 1937 and only sporadic cases have occurred since.

As a case of dermal leishmaniasis is a potential source of danger, and as there are always residual cases of this condition in an endemic area, it will probably never be possible to eradicate kala-azar completely by

means of treatment campaigns, but the disease can apparently be controlled to a great extent, by reducing the sources of infection to a minimum.

In the Mediterranean endemic areas and in China, the evidence is accumulating that dogs act as reservoirs of infection. An attempt should be made to estimate the extent of the infection amongst the local canine community, and, if it is found to be high, a campaign against all stray dogs should be undertaken.

(b) **The transmitting insects.**—The conditions under which sand-flies (*Phlebotomus argentipes*) flourish have been indicated (p. 145).

Damp ground-floor residences should be avoided; no dark corners should be allowed in the rooms and a through draft should be arranged; no vegetation should be allowed close up to the house; all animals should be kept away from the house; a yard or more around the house should be paved with cement and no crevices should be allowed; and chloride of lime should be spread on any uncovered earth near the house to destroy the sand-fly larvæ. The building itself should be of brick and should be kept well pointed. Concrete floors are to be preferred and must be kept in repair. In the case of poorer-class dwellings, it is better to have thin bamboo-matting walls than mud walls or even plastered reeds.

The control of sand-flies in rural areas is very difficult and has yet not become a practicable measure for preventing kala-azar, but the removal of a coolie colony to a new site was practised even before the means of transmission was understood, and the measure proved very successful. By this means the old breeding places of the sand-flies were left behind and it took some time for the flies to establish themselves on the new site. It was however well recognized that if the huts were simply burnt down and rebuilt on the old site, there was no interruption of the kala-azar epidemic.

TREATMENT

Historical.—The history of the treatment of kala-azar can conveniently be divided into three phases: the pre-antimony period, the antimony era, and the new chemotherapeutic era.

The Pre-antimony Period.—Prior to 1915, kala-azar was, it is said, fatal in 95 per cent of cases. This left out of consideration those cases in which the disease disappeared spontaneously; there is indirect evidence that this occurs more often than was previously supposed, but probably 75 per cent of those infected died of the disease within two or three years.

The Antimony Era.—In 1915, Di Cristina and Caronia introduced the treatment by **potassium antimonyl tartrate** given intravenously, a treatment which had been used two years earlier by Vianna and Machado in American mucocutaneous leishmaniasis. This treatment was used in India by Rogers and by Muir later in the same year; later, the former introduced a valuable modification, using the less toxic **sodium antimonyl tartrate**.

In China and the Sudan, on the other hand, the result obtained with the antimonyl tartrates was so poor that these drugs were never used systematically.

The next important advance was the introduction of the **pentavalent antimony compounds**. All the earliest and most of the more successful of these have been prepared by Professor Hans Schmidt. Caronia first used sodium *para*-acetylaminophenyl stibinate clinically in Italy in 1916. After the 1914/18 war, when the preparation was sent out to India, we were less successful with this compound, but many similar compounds were prepared by Schmidt and tested by the writer in India. Of these sodium *meta*-chlor-*para*-acetylaminophenyl-stibinate (Napier, 1923) and diethylamine-*para*-aminophenyl-stibinate (Napier, 1927 and 1932) were successively chosen for more extensive clinical trial; the latter was, until the beginning of the 1939 war when supplies were cut off, very widely used throughout the world under the name neostibosan. In 1922a Brahmachari introduced urea stibamine, another preparation of *para*-aminophenylstibinic acid, which he had prepared in India. A comprehensive account of the antimony preparations used in the treatment of kala-azar and other diseases has been given by Schmidt and Peter.

In 1937, Napier, Chaudhuri, and Rai Chaudhuri first used solustibosan, Bayer 561, a pentavalent compound that can be given intramuscularly and makes a stable solution, so that it can be supplied conveniently in ampoules; in our later experience, we found it less efficacious than neostibosan.

The New Chemotherapeutic Era.—In 1939, Adams and Yorke used 4:4'-diamidino-stilbene in the treatment of a case of kala-azar in England, Adler and Rachmilewitz (1939) in a case of infantile kala-azar in Palestine, Kirk and Sati (1940a) in 8 cases of Sudanese kala-azar, and Napier and Sen (1940) in 8 cases of kala-azar in India, all with very successful results. The writer followed this preliminary report with a report on 100 cases, one quarter of which were antimony-resistant cases (Napier *et al.*, 1942), which showed that this drug was the most powerful that had so far been used in the treatment of the disease.

Recent experience, particularly in the Sudan, seems to indicate that diamidino-stilbene may prove a very toxic drug, but what determines this toxicity is not yet clear. No immediate serious toxic symptoms occurred in any of our hundred cases, but the paræsthesia and dissociated anæsthesia in the area served by the sensory part of the 5th cranial nerve has been so troublesome and so persistent in a majority of our cases that we do not feel justified in using this drug in any but really resistant cases (Napier and Sen Gupta, 1942).

Kirk has also given a short trial to 4:4'-diamidino-diphenoxy-pentane and our results so far with this drug have been very satisfactory. In some twenty odd cases, we have obtained an earlier fall of temperature than with the diamidino-stilbene; the fall of blood pressure appears to be less, but we cannot yet say whether the neuropathy will follow the injections of this preparation also.

Discussion.—As far as India was concerned, the introduction of the antimonyl tartrate constituted a very great advance; the death-rate among treated kala-azar patients was reduced to about 20 per cent, but the treatment was very prolonged, taking from two to three months, patients were very liable not to persist with it, and many relapses occurred.

The advantage of the pentavalent compounds is that they are very much less toxic and can therefore be given in very much larger doses; this means that the duration of treatment can be cut down very materially. They do not cause some of the serious by-effects of the antimonyl tartrates, and consequently the mortality among patients under treatment is very much lower; in our series of more than 500 cases treated by neostibosan, it was only about 2 per cent. By an intensive course of treatment the period in hospital can be reduced to one week.

It is now clear to the writer that kala-azar in Bengal is infinitely more amenable to treatment than is the same disease in other parts of the world. He was at one time inclined to be critical of the methods of other workers, which he judged by their results, and he now fears that these same workers, failing to confirm his results in their own countries, must have questioned his veracity. The writer spent some months in Assam in 1928, and he found that the patients in this province required at least 25 per cent more treatment than his Calcutta patients; he visited China in 1934, and came to the conclusion that at least 50 per cent more treatment was required there; reports on infantile kala-azar in Malta and elsewhere in the Mediterranean indicated that, relative to weight, at least twice as much antimony was required to effect a cure; and reports from the Sudan (Henderson, 1937) show that a very poor cure rate, at the most 50 per cent, could be expected with neostibosan, however much the course of treatment was prolonged.

The aromatic diamidines appear to constitute another advance, as infinitely better results than hitherto have been obtained in the Sudan, and even in Calcutta our previously more successful results have been surpassed; further, excellent results have been obtained in antimony-resistant cases.

Specific treatment

Antimonyl tartrates.—The only reason for using the old form of treatment with the antimonyl tartrates is the higher cost of the new preparations. Relatively unsatisfactory as the former salts are, they are better than no treatment at all, and in poor countries will probably remain in use for many years.

Either the potassium or the sodium salt may be used, but the latter is less toxic. A 2-per-cent solution in physiological saline (0.85 per cent in distilled water) is prepared, and to it 0.5 per cent of phenol is added to prevent the growth of moulds. This solution will keep for some weeks, but it should be examined carefully before it is used, to see that there is no precipitate. For adults the initial dose is 2 c.cm.; this should be increased by 1 c.cm. with each dose up to 5 c.cm.; the injections must be given intravenously, and if the solution leaks into the tissues very severe reactions will follow; injections should be given on alternate days or three times a week, and, as a minimum, twenty-five injections will be necessary.

Coughing, vomiting, and joint pains are common accompaniments of this treatment, and it may be necessary to increase the dosage more slowly or even in some cases to reduce it so as to obviate these symptoms; this prolongs the course of treatment, and the results are correspondingly less satisfactory.

Neostibosan* : di-ethyl para-amino-phenyl stibiate.—This is supplied in sealed ampoules as a light-brown powder, which is dissolved in sterilized distilled water. The strength of the solution is not a matter of great importance, but we generally use 5 per cent for intravenous injections, although strengths up to 25 per cent can be used.

In adults it is better to give the drug intravenously, but in children this is often difficult; it can be given intramuscularly, and then a 25-per-cent solution should be used; this reduces the bulk of fluid and makes an isotonic solution. It should be given into the buttocks on alternate sides; there may be slight local reaction, but often there is none, and abscess formation is very rare. Only one abscess occurred in a series of twenty adults treated with intramuscular injections, and we have never seen an abscess in a child.

Dosage.—The first dose for an adult should be 0.2 and subsequent doses 0.3 gramme. The adult dose can be given to children of 60 pounds or more; about 50 pounds 0.25 gramme, about 40 pounds 0.2 gramme, about 30 pounds 0.15 gramme, and about 20 pounds 0.1 gramme for the maximum dose may be taken as a rough guide to dosage. Children tolerate a relatively larger dose than adults and seem to require it. It may be advisable to modify the dosage in very debilitated patients.

The injections may be given daily or on alternate days, better results being obtained from daily injections.

Length of treatment.—It is extremely difficult to be dogmatic about the length of the course of treatment. A high rate of cures was obtained by giving eight injections on eight consecutive days. Workers in other

* Neostibosan is temporarily off the market, but there seems to be little reason why enterprising drug manufacturers should not make di-ethyl para-amino-phenyl stibiate.

countries, especially those in the Sudan, in China and in some of the Mediterranean areas, have not found that this short course is sufficient (*vide supra*). In any case, if the economic aspect does not predominate, it is probably safer to extend the course to twelve injections; but, when it is a matter of curing the largest number of persons with a given quantity of the drug, eight injections constitute probably the optimal course, according to Indian experience.

Response to treatment.—Little notice should be taken of the immediate response of each patient to the treatment, especially when the daily dosage is adopted, as, at the conclusion of a course of treatment, which the subsequent history of the patient shows was successful, the patient may show very little improvement, even the fever remaining until after the last injection has been given. Although as a rule the temperature comes down after five or six injections, there is seldom much reduction in the size of the spleen until about a fortnight after the beginning of the treatment; it then decreases steadily. Figure 36 shows a characteristic response to treatment in an average case.

After three weeks the spleen should be considerably reduced, the patient should be gaining weight—he may lose weight for the first two weeks—the leucocyte count should be above 6,000 per c.mm.; and he should be free from fever. When he is in this state, the patient is probably cured; if not, he may be going to relapse, and a second course of injections may be necessary. In some cases, however, progress is very slow, and unless there is a definite return of fever, which is not due to some complicating infection, it is probably advisable not to embark too readily on a second course but to wait a few weeks before starting it. In the relapsing case the temperature usually mounts slowly; any sharp rise during the course of treatment is generally due to some coincident infection—malaria being by far the commonest in India. In most

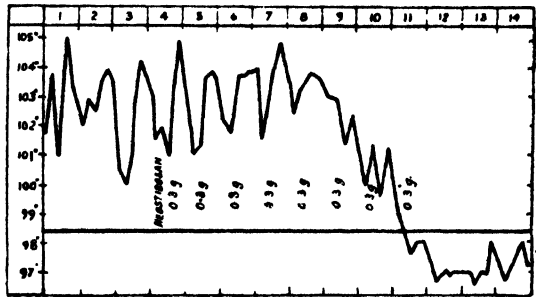


Figure 36 : A characteristic response to treatment in an average case.

cases in which malaria supervenes, it is obvious that the disease must have been latent, and when patients come from a malaria endemic area, it is advisable to give a course of quinine or other anti-malarial drug as a routine when the antimony course is completed.

Patients afebrile at the beginning of treatment not uncommonly show a febrile reaction, in the form of a daily rise of temperature, or a sharp rise after each injection.

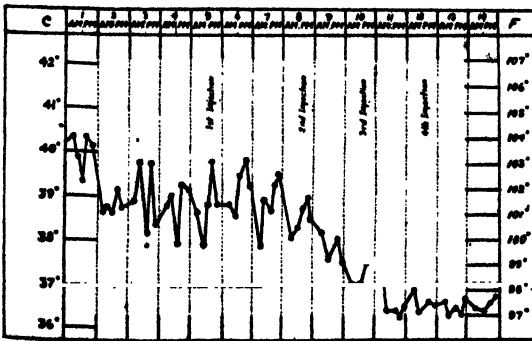


Figure 37 : Early response to neostibosan treatment; the temperature remained normal subsequently.

Urea stibamine.—Urea stibamine has been extensively used in India and in a series of cases treated in our hospital gave very good results. It is slightly more toxic than neostibosan and cannot be given in such large doses; we found that 0.25 gramme was the largest dose that it was advisable to use, but most workers advocate 0.2 gramme as a maximum; the injections should be given on alternate days or three times a week, but not daily. The initial dose recommended is 0.05 gramme, the second 0.1 gramme, the third 0.15 gramme, and the fourth and subsequent doses 0.2 gramme. This drug also is supplied in sealed ampoules; the strength of solution is not important, but, as the solution cannot be sterilized by heating, sterilized distilled water must be used. It should be given intravenously. If allowed to leak into the subcutaneous tissues or if given intramuscularly, it causes much more pain than neostibosan, but not the very severe reactions caused by sodium antimonyl tartrate. The course of treatment is from twelve to fifteen injections.

Other antimony preparations.—Neostam gave satisfactory results in our cases. The dosage is much the same as for neostibosan. Antimosan and foudadin are aromatic trivalent compounds; a cure can be effected with either, but they are not so satisfactory as the pentavalent compounds for the visceral form of the disease, about twenty injections being required.

Complications associated with antimony treatment.—Whereas with the trivalent salts of antimony, coughing, vomiting, joint pains, and the more serious lung complications commonly occur, with the pentavalent compounds, complications are rare. With neostibosan, practically the only complication that ever occurs is a sharp rise of temperature on the day of the injection; this may be accompanied by vomiting. Very rarely this is due to some idiosyncrasy on the part of the patient, and the dosage has to be modified until tolerance is established, but more often it is due to some defect in the solution. We have never traced this to the drug but always to the distilled water in which it is dissolved, since the use of a fresh supply of distilled water has arrested the reactions.

With some of the pentavalent compounds, but very rarely with neostibosan, a condition suggesting **anaphylactic shock** occurs. Usually this does not follow the first injection but one of the later ones, the fifth or sixth, thus suggesting that the patient has been sensitized. This reaction has not been observed when daily injections are given, but has been reported in a few cases in which wider spacing of the injections was adopted. A few minutes after an injection, the patient's face becomes puffy, and an urticarial rash appears all over the body; the voice becomes husky, and the patient has difficulty in breathing; he becomes collapsed, and the pulse is imperceptible at the wrist; he often has diarrhoea and vomiting, and he may become cyanosed and unconscious for a few minutes. Recovery is usually rapid and is accelerated by an injection of solution of adrenaline hydrochloride and the administration of a diffusible stimulant. For the continuance of the treatment, the best course is to employ another compound and to begin with minute doses.

With higher doses of urea stibamine and of some of the other compounds, **hæmorrhages** from the gums, nose, and stomach sometimes occur; we have also seen retinal hæmorrhages, and in one or two cases cerebral hæmorrhages have been suspected.

The aromatic diamidines.—In our present state of knowledge, great caution should be exercised in using these drugs (*vide supra*) and they should be reserved for antimony-resistant cases only. The dosage recommended below is that used by the writer, who has treated well over a hundred cases with 4:4'-diamidino-diphenyl-ethylene (stilbene) and thirty or so with 4:4'-diamidino-diphenoxy-pentane. The immediate reactions described below have been more prominent in the case of the former drug, and the late sequel has only been noted with this drug, but our experience with the latter has been too short and too recent for us to say that the neuropathological sequel described below does not occur.

They are supplied in the form of a white powder in sealed ampoules; this is dissolved in distilled water to make a 1-per-cent solution, and given intravenously. The injections are given daily and very slowly. The **maximum dose** should not exceed 1 milligramme (0.001 gramme) per pound weight of patient. To adults, irrespective of size and condition (because we have found that weak emaciated individuals stand the drug best), we give 0.025 g. as the initial dose. If this is followed by a very severe reaction, we give 0.035 g. next day but precede the dose by an injection of 0.25 c.c.m. of 1 in 1,000 adrenaline; if the reaction is mild, we increase the dose to 0.050 g. but still give the adrenaline; or if there is no reaction we make the next dose 0.050 g. without adrenaline. The doses are increased as rapidly as possible by 0.010 g. or 0.020 g., according to the reactions, up to the maximum, namely 0.001 g. per pound weight of patient to the nearest 0.010 g.; adrenaline is given for the next dose whenever there is a marked reaction to the previous dose, and it is usually possible to omit it after the maximum has been reached.

Children stand the drug better than adults; we usually start with 0.010 g. and increase the dose by 0.005 g. to well over the 0.001 g. per pound maximum. In a few cases we gave the drug **intramuscularly**; it was distinctly painful and caused a sharp local reaction but produced no abscess. The effect seemed to be about as good as when it was given intravenously, but we were slightly bolder with our dosage, as there was practically no general reaction.

We gave 10 injections in the majority of cases. This meant a varying total dose. It is probably safe in our present state of knowledge to aim at a **total dose** of not less than 0.750 g. per 100 pounds weight of patient, and 1.000 gramme for resistant cases. Other workers have recommended a maximum of 0.001 g. per kilogramme, but, in the writer's experience, some of the worst reactions followed the earlier injections which were always small, and, as he found little difficulty in reaching his higher maximum, he considers that it is unnecessary to prolong the course of treatment or alternately to risk having to repeat it. Kirk in the Sudan seems to have given a much more extended course and greater total doses; in his series of 8 cases (Kirk and Sati, 1940a) he obtained cures with total doses varying from 0.975 g. in 24 doses to 4.400 grammes in 70 doses, and in his later report (Kirk and Sati, 1940b) his total dose varied from 0.750 g. to 4.900 g.

The good effects of treatment with the aromatic diamidines are not immediately apparent, and in the vast majority of cases the temperature remains until after the course is complete; in fact in many, the first few injections appear to cause an exacerbation of all the symptoms. The temperature usually falls to normal a day or two after the last injection;

about a week later there is a sudden very rapid decrease in the size of the spleen, and the patient then begins to put on weight (see figures 38, 39 and 40).

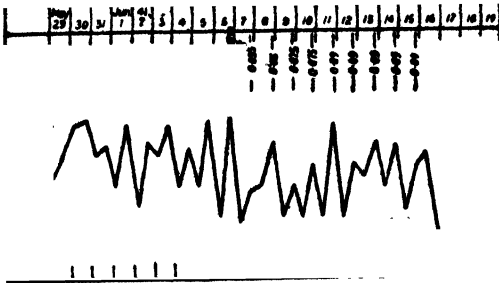


Figure 38 : Response to diamidino-stilbene; no fall of temperature until course is complete, the usual response.

loss of control of the bowels and urine, and loss of conjunctival reflex; in the worst case in the writer's experience, the patient, a well-developed and healthy-looking man with no discoverable abnormality except an oriental sore, who had received a dose of less than 0.0005 gramme per pound body weight, remained unconscious for about an hour, but recovered completely in another hour or so.

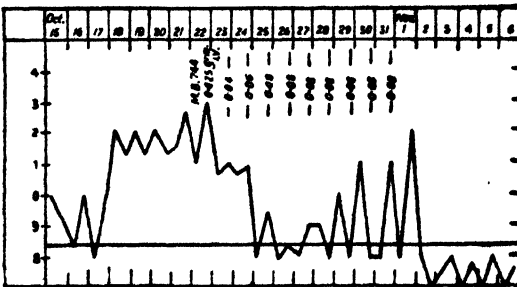


Figure 40 : Response to diamidino-stilbene; very early fall usually results in a subsequent febrile reaction.

The reactions and

Some reactions will be noticed in almost every case. The mild reactions include a headache, flushing of the face, sweating, and a burning sensation all over the body. In the more severe cases the headache will be intense, there will be giddiness, faintness, palpitations, and epigastric pain and vomiting. The most severe symptoms will be collapse, unconsciousness,

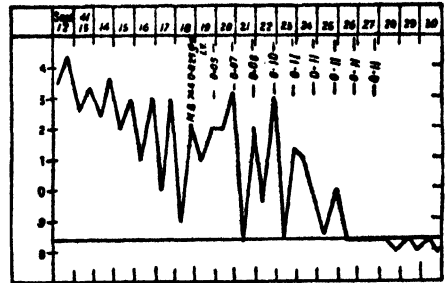


Figure 39 : Response to diamidino-stilbene; earlier fall of temperature.

As noted above, most of these symptoms can be obviated, or reduced to a minimum, by a small dose of adrenaline before the injection of the drug, and a moderate dose after the injection will usually relieve the patient rapidly. Where vomiting is prominent, this can be reduced to some extent by giving the drug on an empty stomach, but otherwise it is better to give it not more than two hours after a meal.

In about twenty cases, that is in over half the patients actually seen by us subsequently, a curious neuropathy occurred, namely, a subjective disturbance of sensation over various parts of the trigeminal nerve area, hyperæsthesia, paræsthesia, anæsthesia, and formication, and loss of sensation to light touch but preservation of the sense of pressure and pain. The first symptom is usually numbness of the area and is noticed about three months after the course is completed. The condition has persisted in one case for nearly two years; it showed little increase from the time we first saw the patient, five months after discharge from hospital, and has now decreased slightly (see figure 41).

Several patients have been treated with large doses of aneurin without effect, but subjective improvement has appeared to follow the (empirical)

administration of cobra venom, intramuscularly, in doses of 0.1 c.cm. rising to 1.0 c.cm. 1 in 100,000, every third day, in a number of cases.

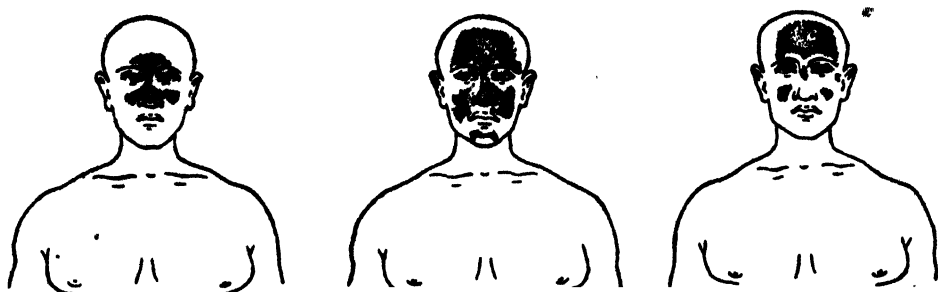


Figure 41 : Affected areas in three cases of post-diamidino-stilbene neuropathy.

Subsidiary treatment

Very little subsidiary treatment is of any value until the course of specific has been completed; indeed, whatever other treatment is given, nothing should be allowed to interfere with the course of injections once they have been begun. When there are complicating infections, such as malaria, and hookworm disease, the kala-azar should be treated first. It has been suggested that heavy hookworm infections diminish the effect of the specific kala-azar treatment; there is no evidence that this is the case, but treatment of the hookworm infection should always be delayed until one course of antimony has been given, though it is not necessary to wait to see if the cure of the kala-azar is complete.

The blood picture will soon return to normal, but this may be accelerated by a course of ferrous sulphate, 9 grains a day for two weeks. In cool climates or in the cold weather in India, malt and cod-liver oil and in the hot weather, compound syrup of hypophosphites, or some other suitable tonic, should be given during convalescence.

Diet.—As a rule it is not necessary to enforce any severe dietary restrictions unless this is indicated by special symptoms. Some patients are always attacked by diarrhoea when allowed a full diet, and when the fever is at its height it is inadvisable to allow a high protein diet; but most patients have a good appetite and do well on a liberal diet. Our hospital patients are allowed an ordinary diet unless there is some special contra-indication, but for out-patients and others not immediately under control, a vegetarian diet with only a little rice, plenty of milk, and eggs is recommended.

Treatment of complications.—Practically there are no complications which warrant the discontinuance of the specific treatment, frank pneumonia being possibly the exception. In the presence of *cancrum oris*, the specific treatment should be begun immediately, and the injections given daily. The mouth should be kept as clean as possible with a solution of hydrogen peroxide, eusol, or other mild antiseptic lotions; vigorous local treatment with strong antiseptics should be avoided. Plastic surgery may eventually be necessary to replace lost tissue.

Treatment of resistant cases.—Other complications should be treated symptomatically. A resistant case may be defined as one in which a cure is not effected by an ordinary course of treatment which will cure from 90 to 95 per cent of patients; it is therefore a relative term, but nevertheless

patients seem to be divided fairly sharply into two classes, the ordinary and the resistant. When a patient who has a clear history of having had a full course of treatment a month or two before is found still to have a visceral infection, he should be classed as a resistant case and treated accordingly.

Early experience with the aromatic diamidines indicates that these are the drugs of choice in resistant cases. We have prolonged the course to 12 or 15 injections in resistant cases; with a mean total dose of 0.919 g. and a mean relative dose of 1.048 g. per 100 lb. of body-weight of patient, we cured (apparently) 22 out of 25 antimony-resistant cases.

Previously, the course of neostibosan that we gave in a resistant case (adult) was as follows :—

Twelve injections in twelve days, beginning with 0.2, followed by 0.3, 0.4, and subsequently 0.5 gramme daily; an interval of twelve days; a second series of twelve injections, beginning with a dose of 0.3 gramme; another interval of twelve days; and a third series of twelve injections beginning with 0.3 gramme.

If the patient shows little sign of improvement during the first series of injections, it is advisable to give one or two turpentine injections during the second series. Muir's prescription for the turpentine injections is : 1 part each of turpentine, camphor, and creosote, and 2½ parts of olive oil. Of this, 1 c.cm. is injected into the gluteal muscle; if a sharp reaction does not occur, a larger dose is injected a day or two later. The object is to produce a very severe local reaction. The turpentine injections are given coincidentally with the antimony injections.

In one of the most resistant cases the writer has ever encountered, a cure was effected by the application of the same principle in a slightly more primitive form by a practitioner of the 'indigenous' system of medicine who placed a vesicatory plaster on the patient's abdomen which caused the whole abdominal wall down to the muscle to slough and left a deep ulcer the size of the palm of the hand; when the ulcer healed the kala-azar was cured.

When one antimony compound has been used throughout without success, a change to another compound should be tried.

Treatment of post-kala-azar dermal leishmaniasis.—Antimony seems to be the only specific for post-kala-azar dermal leishmaniasis, but a cure is not nearly so readily effected as in the visceral form of the disease. Preliminary experience with diamidino-stilbene does not suggest that it is of any value in this condition. We have generally used one of the pentavalent compounds, but in a few obstinate cases good results have followed the use of the newer trivalent compounds, antimosan and foudadin.

The ordinary course of injections, as recommended for the visceral infection, should be given, but the injections should be on alternate days or even more widely spaced. One course may be sufficient. The nodular lesions will usually show distinct improvement during the first course of injections, but the hypo-pigmented lesions usually remain unchanged, gradually regaining their pigment during the course of a month or so. Similarly, the shrinking in the nodular lesions will continue for some time after the end of the course of treatment; a period of at least two months should therefore be allowed before it is decided that another course will be necessary.

Injection of a 2-per-cent solution of berberine sulphate into the nodular lesions is usually followed by their shrinkage, but this is not a very

practical method when lesions are extensive. We have seen a few cases improve on large doses of potassium iodide, given up to the point of producing iodism, especially cases in which the nodular lesions were very extensive; the nodules may undergo ulceration, but heal rapidly when the potassium iodide is discontinued.

PROGNOSIS

Opportunities for watching the progress of the untreated disease have now gone, but in the past temperature records have been kept for a year and longer. Periods of high remittent fever were followed by periods of almost complete absence of fever, the complete cycle taking from a month to two months. The average duration of the disease was about two years, but many cases were reported in which it seemed to enter upon a chronic stage without any symptoms except slight anæmia and great splenomegaly.

Death usually occurs from some complicating infection, such as dysentery or pneumonia, or from cancrum oris. In infants and young children the disease runs a far more acute course, and the duration is often less than six months.

Rarely, in India at least but apparently much more frequently in other countries, especially in the Sudan, the disease runs a much more rapid course; after two or three months of high fever, purpuric spots appear, there are profuse hæmorrhages from the mucous membranes, and death follows rapidly.

From experience in India, the prognosis can be summarized as follows : if no treatment at all is given, 75 per cent of patients will die, the majority within a period of two years. In the infantile form the natural duration of the disease is shorter, probably about a year. If a full course of treatment with either neostibosan or urea stibamine is given between the third and about the twelfth month of the disease, from 90 to 95 per cent will be completely cured of the visceral infection, about 2 per cent will die of some intercurrent infection during the course of the treatment, and the rest will relapse. Of those that relapse, i.e. of the resistant cases, about half to two-thirds will be cured by subsequent treatment, but there will be a small residue of entirely resistant cases. The new drug diamidino-stilbene promises a higher cure rate, especially amongst antimony-resistant cases. In a series of one hundred cases of which a quarter were resistant cases, there were two deaths and five relapses, that is to say an apparent cure rate of 93 per cent.

If the disease has lasted more than a year, the patient may be very weak and emaciated and have developed various complications, e.g. cirrhotic changes in the liver. Although uncomplicated cases of long duration usually respond well to treatment, on the whole the prognosis is not quite so good at this stage. Jaundice appearing late in the disease, and ascites are bad prognostic signs. Amongst the cases treated during the first three months of the disease, a slightly higher initial relapse rate may be expected, but there is no evidence that such cases become antimony-resistant more readily.

In Bengal, in about 5 per cent of treated cases, post-kala-azar dermal leishmaniasis develops. This sequel is apparently much rarer, or even unknown, in other localities.

REFERENCES

- ADAMS, A. R. D., and YORKE, W. Studies in Chemotherapy, XXIII. A Case of Indian Kala-azar treated with 4:4'-Diamidino Stilbene. *Ann. Trop. Med. and Parasit.*, **33**, 323.

- ADLER, S. (1940) .. Attempts to Transmit Visceral Leishmaniasis to Man: Remarks on Histopathology of Leishmaniasis. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **33**, 419.
- ADLER, S., and RACHMILEWITZ, M. (1939). A Note on the Treatment of a Case of *Leishmania infantum* with 4:4'-Diamidino Stilbene. *Ann. Trop. Med. and Parasit.*, **33**, 327.
- ADLER, S., and THEODOR, O. (1931) . Investigations on Mediterranean Kala-azar. *Proc. Roy. Soc., Ser. B.*, **103**, 494.
- BOUSFIELD, L., THOMSON, D. S. B., and MARSHALL, W. E. (1911). Remarks on Kala-azar in the Kassala and Blue Nile Districts of the Sudan. *Fourth Rep. Wellcome Trop. Res. Lab. at the Gordon Memorial College, Khartoum*. Vol. A pp. 127, 143 and 157. Baillière, Tindall and Cox, London.
- BRAHMACHARI, U. N. (1922) .. A New Form of Cutaneous Leishmaniasis—Dermal Leishmanoid. *Indian Med. Gaz.*, **57**, 125.
- Idem* (1922a) .. Chemotherapy of Antimonial Compounds in Kala-azar Infection. *Indian J. Med. Res.*, **10**, 492.
- COCHRANE, S. (1912) .. The Superficial Lymph-Nodes as a Source of Leishmania for Diagnosis in Cases of Kala-azar. *J. Trop. Med. and Hyg.*, **15**, 9.
- DE, M. N. (1934) .. A Study on the Parasites of Kala-azar and Their Distribution in the Body. *Indian J. Med. Res.*, **21**, 627.
- FORKNER, C. E., and ZIA, L. S. (1934). Viable *Leishmania donovani* in Nasal and Oral Secretions of Patients with Kala-azar and the Bearing of this Finding on the Transmission of the Disease. *J. Exper. Med.*, **59**, 491.
- GILES, G. M. (1892) .. Notes on Anchylostomiasis, being for the most part, a résumé of a Report on the Diseases known in Assam as Kala-azar and Beriberi. *Indian Med. Gaz.*, **27**, 170, 193.
- HENDERSON, L. H. (1937) .. Clinical Observations on Kala-azar in Fung Province of Sudan. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **31**, 179.
- HINDLE, E., HOU, P. C., and PATTON, W. S. (1926). Serological Studies on Chinese Kala-azar. *Proc. Roy. Soc., Ser. B.*, **100**, 368.
- KIRK, R., and LEWIS, D. J. (1940) .. Studies in Leishmaniasis in Anglo-Egyptian Sudan; Sandflies (Phlebotomus) of Sudan. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **33**, 623.
- KIRK, R., and MACDONALD, D. R. (1940). An Unusual Case of Leishmaniasis treated with 4:4'-Diamidino Diphenoxy Pentane. *Ann. Trop. Med. and Parasit.*, **34**, 131.
- KIRK, R., and SATI, M. H. (1940) .. Studies in Leishmaniasis in Anglo-Egyptian Sudan, Punctate Rash in Treated Cases. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **34**, 213.
- Idem* (1940a). Notes on Some Cases of Sudan Kala-azar treated with 4:4'-Diamidino Stilbene. *Ann. Trop. Med. and Parasit.*, **34**, 83.
- Idem* (1940b). The Use of Certain Aromatic Diamidines in the Treatment of Kala-azar. *Ann. Trop. Med. and Parasit.*, **34**, 181.
- KNOWLES, R., NAPIER, L. E., and SMITH, R. O. A. (1924). On a Herpetomonas found in the Gut of the Sandfly, *Phlebotomus argentipes*, fed on Kala-azar Patients. *Indian Med. Gaz.*, **59**, 593.
- LLOYD, R. B., and NAPIER, L. E. (1930). The Blood-meal of Sandflies Investigated by means of Precipitin Antisera. *Indian J. Med. Res.*, **18**, 347.
- MACKIE, F. P. (1914) .. Kala-azar in Nowgong (Assam). *Indian J. Med. Res.*, **1**, 626.

- NAPIER, L. E. (1923) .. The Treatment of Kala-azar by Meta-Chlor-Para-Acetyl-Amino-Phenyl Stibiato of Sodium (von Heyden 471), 11 Cases. *Indian Med. Gaz.*, **58**, 578.
- Idem* (1927) .. The Pentavalent Compounds of Antimony in the Treatment of Kala-azar : Part II. *Indian J. Med. Res.*, **15**, 181.
- Idem* (1932) .. The Pentavalent Compounds of Antimony in the Treatment of Kala-azar : Part VII. *Indian J. Med. Res.*, **19**, 719.
- Idem* (1936) .. Technique of Spleen Puncture. *Lancet*, **ii**, 126.
- NAPIER, L. E., CHAUDHURI, R. N., and RAI CHAUDHURI, M. N. (1937). A Stable Solution of Antimony for the Treatment of Kala-azar. *Indian Med. Gaz.*, **72**, 462.
- NAPIER, L. E., and DAS GUPTA, C. R. (1934). Further Clinical Observations on Post-Kala-azar Dermal Leishmaniasis. *Indian Med. Gaz.*, **69**, 121.
- NAPIER, L. E., KIRWAN, E. O'G., and SEN, G. (1941). Eye Complications of Dermal Leishmaniasis. *Indian Med. Gaz.*, **76**, 542.
- NAPIER, L. E., and KRISHNAN, K. V. (1931). A Theory of the Etiology and Epidemiology of Kala-azar in India. *Indian Med. Gaz.*, **66**, 603.
- NAPIER, L. E., and HENDERSON, J. M. (1931). The Erythrocyte Sedimentation Rate in Kala-azar. *Indian J. Med. Res.*, **19**, 691.
- NAPIER, L. E., and SEN, G. N. (1940). Diamidino-Stilbene in the Treatment of Kala-azar. *Indian Med. Gaz.*, **75**, 720.
- NAPIER, L. E., SEN GUPTA, P. C., and SEN, G. N. (1942). The Treatment of Kala-azar by Diamidino Stilbene : Analysis of 101 Cases. *Indian Med. Gaz.*, **77**, 321.
- NAPIER, L. E., SMITH, R. O. A., DAS GUPTA, C. R., and MUKERJI, S. (1933). The Infection of *Phlebotomus argentipes* from Dermal Leishmanial Lesions. *Indian J. Med. Res.*, **21**, 173.
- D'OELSNITZ, M. (1938) .. Early Diagnosis, Treatment and Prophylaxis of Kala-azar. *Mouvement Sanitaire*, **15**, 220. (Abstract—*Trop. Dis. Bull.*, **35**, 869.)
- ROGERS, L. (1897) .. Report of an Investigation of the Epidemic of Malarial Fever in Assam, or Kala-azar, Shillong.
- Idem* (1908) .. *Fevers in the Tropics*. Oxford University Press, London.
- ROSS, R. (1899) .. Infectiousness of Malarial Fever and Kala-azar. *Indian Med. Gaz.*, **34**, 233.
- SCHMIDT, H., and PETER, F. M. (1938). *Advances in the Therapeutics of Antimony*. George Thieme, Leipzig.
- SHORTT, H. E. (1923) .. *Herpetomonas stenoccephali*, Fantham. Some Observations on its Life History and Reactions to Different Environments. *Indian J. Med. Res.*, **10**, 721.
- SHORTT, H. E., BARRAUD, P. J., and CRAIGHEAD, A. C. (1926). Note on a Massive Infection of the Buccal Cavity of *Phlebotomus argentipes* with *Herpetomonas donovani*. *Indian J. Med. Res.*, **14**, 329.
- SHORTT, H. E., SMITH, R. O. A., SWAMINATH, C. S., and KRISHNAN, K. V. (1931). Transmission of Indian Kala-azar by the Bite of *Phlebotomus argentipes*. *Indian J. Med. Res.*, **18**, 1373.
- SMITH, R. O. A., and HALDER, K. C. (1935). Some Observations on Dermal Leishmaniasis. *Indian Med. Gaz.*, **70**, 544.
- SMITH, R. O. A., HALDER, K. C., and AHMED, I. (1941). Further Investigations on the Transmission of Kala-azar. *Indian J. Med. Res.*, **29**, 799.
- STEPHENSON, R. W. (1940) .. An Epidemic of Kala-azar in the Upper Nile Province of the Anglo-Egyptian Sudan. *Ann. Trop. Med. and Parasit.*, **34**, 175.
- SWAMINATH, C. S., SHORTT, H. E., and ANDERSON, L. A. P. (1942). Transmission of Indian Kala-azar to Man by the Bites of *Phlebotomus argentipes*, Ann. and Brun. *Indian J. Med. Res.*, **30**, 473.
- YOUNG, C. W., and HERTIG, M. (1926). The Development of Flagellates in Chinese Sandflies (*Phlebotomus*) fed on Hamsters infected with *Leishmania donovani*. *Proc. Soc. Exper. Biol. and Med.*, **23**, 611.

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Definition.—Cutaneous leishmaniasis or oriental sore (also known as Baghdad boil, Aleppo boil, Delhi boil, Biskra button, Lahore sore, and by many other local names) is a specific granuloma of the skin which usually breaks down to form a large indolent ulcer; the lesions are more often multiple but may be single and are usually on exposed parts of the body; they are caused by a protozoal parasite, *Leishmania tropica*, which is transmitted from host to host by a sand-fly of the genus *Phlebotomus*.

EPIDEMIOLOGY

Geographical distribution.—Oriental sore is more widely distributed throughout the world than any of the other leishmania infections.

In Europe, several cases have been reported from Italy, most of them from the southern portion of the peninsula; Pulvirenti also recorded cases from Calabria and from several districts in Sicily, from Palermo on the north coast to Catania on the south and Caltanissetta inland. The disease is very common in Crete, and isolated cases have been reported from northern Italy, from the east coast of Spain, and from the Eastern Pyrénées in France.

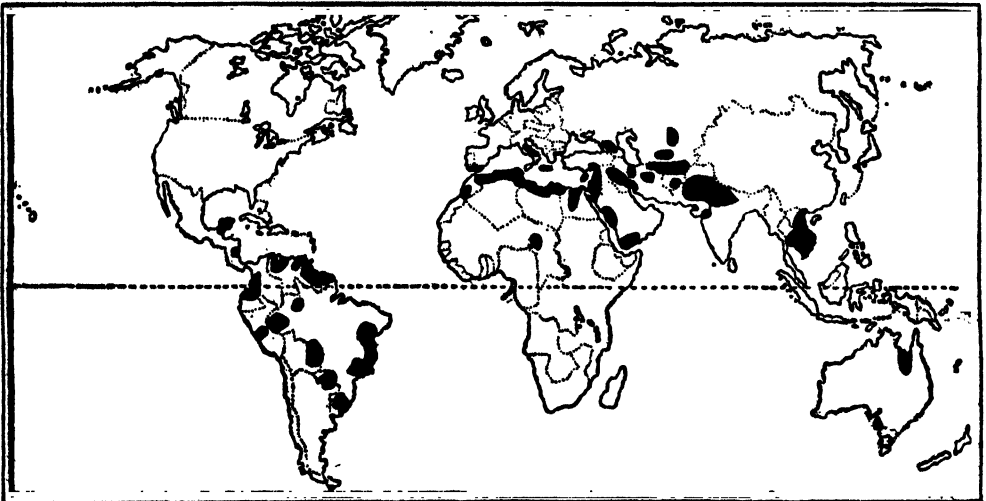


Figure 42 : Distribution of espundia and oriental sore; the former is confined to the American continent, and the latter to the Old World.

There are certain endemic foci in northern Africa, notably at Gafsa in Tunis, Biskra in Algeria, and Bonanane in Morocco, but the whole of these countries would appear to be endemic areas, since sporadic cases are reported from time to time. Most of the endemic foci are inland and well away from the endemic areas of kala-azar, but in some places both diseases occur. Cases have been reported from Egypt, the Sudan, Souf in the Sahara, the French Congo, Nigeria, and Angola in West Africa.

The incidence is very widespread in Asia; sporadic cases have been recognized in various parts of Asia Minor; Aleppo is an endemic focus; further south many cases have been reported from Palestine, Jericho and Kantara being the main endemic foci; the disease occurs in Transcaucasia; in Turkmenistan, Termeze, Bokhara, Samarkand, and Askabad are mentioned as endemic foci; and Agronick (1925 and 1927) reported cases in Transcaspia; the disease occurs in Iran, especially southern Iran, and in Iraq, where Baghdad is an endemic focus.

In India, the disease is found over the whole of the western and drier portion of the Indo-Gangetic plain; the endemic area extends north into the North-West Frontier Province and Baluchistan and down the west coast of the peninsula as far as Cambay in the Bombay Presidency and east as far as Delhi; further east as far as Benares sporadic cases are reported.

In Oceania, instances of oriental sore have been reported from North Queensland.

Distribution of oriental sore compared with that of kala-azar.—Kala-azar and oriental sore are very rarely present in the same locality; both diseases occur in Crete, and in some parts of Asia Minor they occur side by side and in fact are reported to have appeared simultaneously in the same family. In India, oriental sore is found in the dry western half of the Indo-Gangetic plain, whereas kala-azar is confined to the moist eastern portion of this plain; in no one place in India are both diseases truly endemic, although from a few places in the central portion of this plain, e.g. Benares, sporadic cases of both diseases have been reported. This natural segregation of the two diseases led Manson to suggest that cross immunity took place and that protective inoculation with the comparatively benign oriental sore might prove a protection against the then deadly kala-azar. It has now been satisfactorily shown that cross immunization does not occur.

The distribution of the two diseases is easily explained on the grounds of sand-fly distribution, the common sand-fly of the moist areas being *Phlebotomus argentipes*, the proved transmitter of kala-azar, whereas *P. papatasi* and *P. sergenti*, which probably transmit oriental sore, are common sand-flies of the dry areas.

Climatic factors.—It would be difficult to correlate the various climatic conditions in the endemic areas, and, as they are so widespread, it seems improbable that there are many climatic factors common to these areas. Most of the areas of greatest activity, however, lie between latitudes 20° and 45°N. These areas have a very hot season, some of them as hot as in any part of the world, and a short cold season in which the night temperature occasionally falls as low as zero. Most of them are dry areas in which there is little vegetation, and many of them border on desert land. In northern Africa they are inland rather than on the coast, and the disease is usually associated with a rocky soil. In India, the disease appears to be confined largely to the alluvial areas of the western portion of the Indo-Gangetic plain.

Epidemic features.—In the areas where it occurs the disease is usually endemic, but the incidence varies considerably from year to year, and very frequently assumes epidemic proportions.

An epidemic of oriental sore in the neighbourhood of Aleppo occurred when some refugees occupied a new partly cleared site on which they erected mud and straw-brick huts. Out of a total of 127 families, 45 were affected, 78 individuals having sores. The site abounded with sand-flies; when the clearing of the new site was complete, the number of sand-flies decreased and the incidence of oriental sore fell.

In Quetta, after the earthquake, where the debris provided ideal conditions for breeding of sand-flies, there was an epidemic of oriental sore amongst the troops who helped to clear the area.

In 1939-40 there was an epidemic in an insanitary area on the outskirts of Delhi in which it is estimated that 15,000 to 20,000 persons were affected (Shah, 1941).

Dostrowsky in Palestine reported that family incidence was considerable, but this has not been the experience of many other observers, and in areas where the disease is sporadic it is by no means uncommon in a family of children for one child alone to be infected.

Seasonal incidence.—Practically all observers have noted that there is a definite season of onset, but this season is not identical in the various endemic areas. Dostrowsky reported that in Palestine in most cases the lesions first appeared between the months of September and April, i.e. immediately before and during the rainy season. Cartron and Bacqué said that most of the cases in northern Africa were infected in July, August and September. Yakimoff and Schockov reported that out of 48 cases seen in Turkestan in January, in one case the sores appeared in June, in 7 in July, and in 40 in August. In Iraq, the first cases are usually seen in July; the monthly incidence rises up to September or October, after which it begins to fall. In the North-West Frontier Province and in the Punjab the first cases appear in June and July; August and September are the months of the highest incidence. A report on oriental sores acquired in Quetta (Goodall) suggested that there the months of maximal infection were September and October. The month of infection, or, if about three months is allowed as an incubation period, the first appearance of the lesions, usually corresponds with the maximum sand-fly incidence.

Age, race, and sex incidence.—Persons of all ages and races and of both sexes appear to be equally susceptible. In the heavily infected areas, children form the bulk of the patients, but this is only because the adults have acquired a degree of immunity from having been infected and cured during childhood. For the same reason foreigners in endemic areas appear to be particularly susceptible.

ÆTIOLOGY

Historical.—The causal organism was first observed in Calcutta by Cunningham (1885), who described a parasite which he had seen in the tissues of an oriental sore in a patient who had come from Delhi. The plate which accompanied his paper leaves little doubt about the nature of the parasites which he observed, but not unnaturally at that early date he was ignorant of the true nature of the bodies that he saw. In 1898, Borowsky recognized the parasite and described it, but his paper, which was written in Russian, was overlooked, and the credit for the first accurate description is usually given to J. H. Wright. Wright (1903) described the parasite which he had recovered from the tissues of an oriental sore in an Armenian immigrant in Boston; he suggested the name *Helcosoma tropicum*. Marsinowsky and Bogrow (1904) described the organism which they had found in an ulcer in a boy from Iran and suggested the name *Ovoplasma orientale*. Nicolle and Sicre (1908) were the first to cultivate the organism and thus to demonstrate its true nature and its relation to *Leishmania donovani*.

The causal organism.—*Leishmania tropica* (Wright, 1903) is a protozoon of the family Trypanosomidæ; it is indistinguishable morphologically and culturally from *L. donovani*, the causal organism of kala-azar; serologically, however, Noguchi was able to distinguish the two parasites. In the tissues of the mammalian host the parasite appears in the 'round' form and has a local distribution, namely, in the endothelial cells in the granulomatous tissue at the margins and in the base of the ulcer, where it is usually found in large numbers. In its arthropod hosts, *Phlebotomus sergenti* and *P. papatasi*, and also in culture medium it passes into its flagellate (leptomonad) form. A few writers have reported invasion of the blood stream by *Leishmania tropica*, but this observation has not been supported generally, and, if this does occur, it must be a rare accident. On the other hand, extension of the infection along lymphatic channels sometimes follows and results in a chain of ulcers along the course of the vessel (see plate VIII, figure 8).

In some small animals a generalized blood infection occurs.

Transmission.—Attention was first focused on the sand-fly as a possible transmitter by Wenyon (1911), who found 6 per cent of the sand-flies in Aleppo, an endemic area, infected with a leptomonad. Work on sand-flies was continued by the Sergeants and others during the next few years, but no very important observation was made. In 1919 Acton, by making comparative anatomical 'spot' diagrams of oriental sores and of sand-fly bites and showing the marked similarity between these diagrams, added further support to the sand-fly hypothesis (see figures 43 and 44).

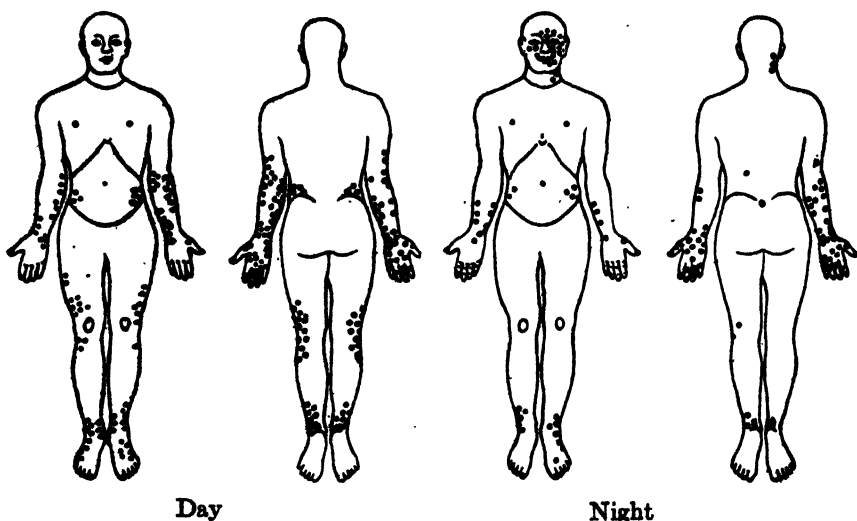


Figure 43 : Spot diagram of the position of sand-fly bites during the day and night.

Sergeant, Sergeant, Parrot, Donatien and Béguet (1921) produced oriental sore in volunteers in a non-endemic area by inoculating crushed sand-flies, *P. papatasi*, collected in an endemic area. This work was elaborated by Adler and Theodor (1926), who carried out numerous experiments with both naturally infected and laboratory infected sand-flies, both *P. papatasi* and *P. sergenti*, which proved conclusively that these sand-flies were natural carriers of *L. tropica*, and that in special circumstances they were capable of transmitting the infection from host to host. In Italy, *P. macedonicum* has been incriminated as the transmitter.

More recently, Adler and Ber (1941) have actually produced 28 oriental sores in 5 volunteers by the bites of artificially infected sand-flies.

The mechanism of transmission is believed to be similar to that of kala-azar. The sand-fly becomes infected by feeding on the indurated edge of the sores of an infected person, or on an animal; sand-flies have been shown to be attracted to the indurated area surrounding a sore, particularly in dogs where the sores are mainly around the eyes and nose; the development of the flagellate form takes place in the fly and the infection moves forward towards its mouth parts, so that, if the fly lives long enough for full development to take place, it will convey the infection when it again feeds on a new host.

It is known that direct inoculation from a sore can produce the lesion, and it is certain that in nature this sometimes occurs, but it is equally certain that it is not the main mode of transmission.

Animal reservoirs.—The sporadic incidence of oriental sore has suggested that there is some non-human reservoir of infection, and lizards

have been suspected in this connection; but there is little evidence to support this view. On the other hand, in some of the endemic areas, *e.g.* Baghdad, Aleppo, and Teheran, dogs are heavily infected and probably act as reservoirs. Many other animals, *e.g.* cats and bears, have been found infected in nature. In certain animals, as well as producing local lesions, *Leishmania tropica* causes a generalized infection, so that it is possible that sand-flies may become infected by simply feeding on the blood of infected animals. In Turkmenistan, the gerbil, *Rhombomys opimus*, has been found infected in nature, to the extent of 60 per cent of specimens examined. Thirty-five per cent of sand-flies living in their burrows have been found infected. These animals therefore obviously play an important part in the ætiology of the disease in desert areas.

Immunity.—Some immunity against subsequent attack is conferred on the patient. This is demonstrated in the epidemiology of the disease by the fact that in endemic areas the indigenous adult is comparatively immune, most of the sufferers being children and immigrants. Advantage has been taken of this fact, and in certain countries women have inoculated themselves with oriental sore on some covered part of the body as a prophylactic against the disfiguring effect of a sore on the face. That this immunity is not complete is shown by the facts that auto-inoculation is not uncommon and that second attacks sometimes occur after the original ulcers have healed completely; of forty-eight cases seen by Yakimoff and Schockov in Turkestan eight had been attacked previously; Marzinowsky and Schourenkoff stated that experimentally produced sores in man only conferred immunity when they ran their natural course, abortive lesions and those subjected to treatment at an early stage failing to produce immunity. It is also claimed that there are different strains of *L. tropica*, and that immunity is not complete against heterologous strains.

There is no reason to suppose that oriental sore confers immunity against other leishmania infections; although there are few areas where both kala-azar and oriental sore are endemic, instances have been reported in which a person suffered from kala-azar after having suffered from oriental sore (Patton, 1922).

PATHOLOGY

The infection is a localized one and there is no general reaction to infection. A very definite tissue reaction is caused by the local presence of the parasite, the macrophage apparently playing the main part in this reaction. Considerable infiltration of all the layers of the dermis by these cells, many of which contain parasites, extends into the subcutaneous tissues. Giant cells are sometimes present. The parasites apparently have a special affinity for the endothelial cells of the arterioles and capillaries, which become parasitized and swollen: the channels become blocked, and necrosis may follow. The cellular proliferation continues and spreads centrifugally, interfering further with the blood supply of the epidermis and reducing it by pressure to a thin membrane which is easily damaged by trauma.

Pyogenic organisms eventually find their way through this damaged epidermis, and ulceration occurs. The pyogenic organisms invade the granuloma and tend to destroy the leishmania parasites. The histological picture then undergoes a change and becomes more like that of an ordinary pyogenic ulcer. At the base of the ulcer the specific granulomatous condition still exists; consequently healing is delayed. The margins of the ulcer show considerable thickening of the epidermis and occasionally

down-growths from the epithelium. *Leishmaniae* do not invade the epidermis.

Eventually the granuloma is invaded and superseded by fibrous tissue and, when the superficial septic process resolves, the epithelium grows in from the edges of the ulcer; a scar, consisting of a thin covering of epithelium over hard fibrous tissue, is left.

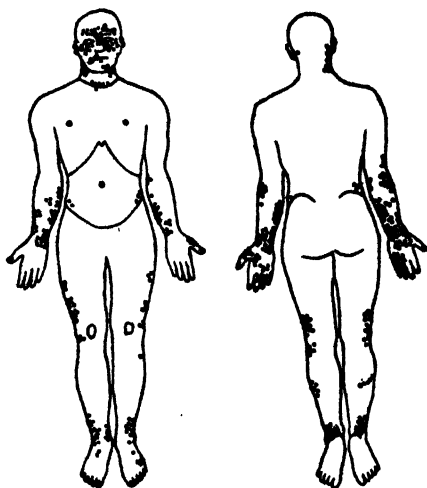


Figure 44 : Spot diagram of the sites of sores in Indian troops in Iraq.

exposed parts of the trunk. The scalp, the palms of the hands, and soles of the feet are not affected. A 'spot' diagram (after Acton) shows the distribution of the sores in Indian troops in Iraq; these soldiers wore 'shorts' and puttees, i.e. their knees were bare (see figure 44).

Number of sores.—The sores are sometimes single, but more often multiple. Occasionally very many sores appear on different parts of the body; figure 4 (plate VIII) shows a patient with 239 sores.

Absence of general symptoms.—As a rule general symptoms do not accompany the appearance of the local lesions, but in some cases there is a history of slight fever lasting a few days.

The typical sore.—A small itching red papule surrounded by a narrow pink halo is first observed at the site of inoculation; this increases in size and an exudate from it forms a scab of dry scales that vary in colour from a whitish to a dark reddish brown; the lesion increases in size and may develop into an ordinary boil or carbuncle, or into a large raised fleshy nodule. In either case the centre of the lesion usually breaks down under the scab and an ulcer forms; the ulcer which is small at first spreads but is usually more or less circular, has clean-cut edges, a

VIII

Fig. 1.—Fungating sore on cheek.

Fig. 2.—Sores commencing to heal.

Fig. 3.—One month later, now completely healed; repigmentation commencing in left hand.

Fig. 4.—Patient with 239 sores.

Fig. 5.—*Leishmania tropica* in an endothelial cell.

Fig. 6.—A clean sore commencing to heal.

Fig. 7.—A fungating sore with eczematous areolar.

Fig. 8.—Ulcerating sore on finger with lymphatic spread; nodules appearing along the course of the lymphatics.

[Figures 2 and 3 after Goodall (1937): others after Shah (1941).]



Fig. 1

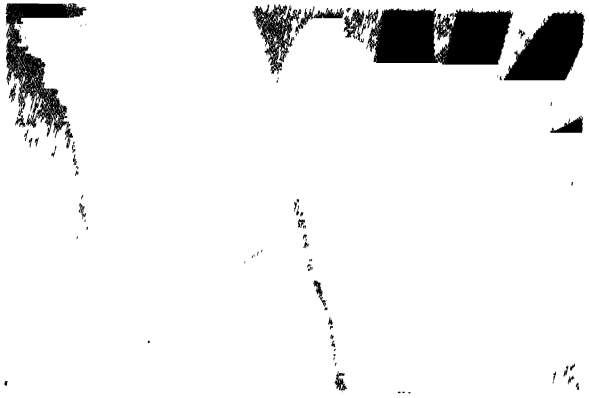


Fig. 2

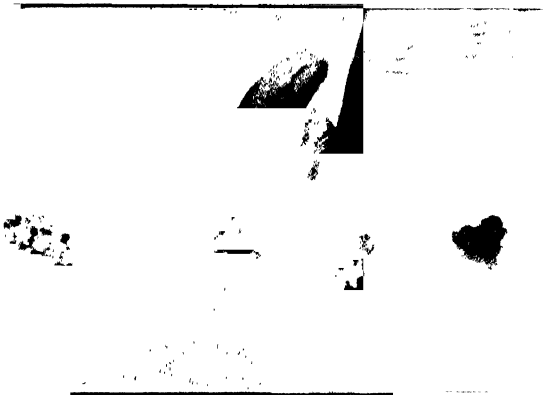


Fig. 3



Fig. 4



Fig. 5

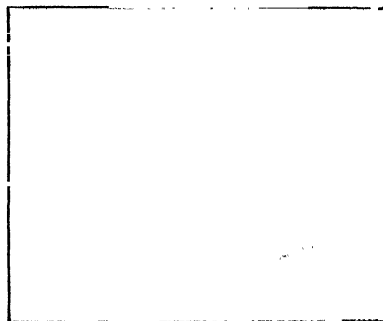


Fig. 6



Fig. 7



sloughing and later a granulating base, and is surrounded by an area of red induration about a quarter of an inch in breadth. The ulcer exudes a sero-purulent discharge which may dry and fill the ulcer with a hard dry scab which is difficult to remove. If it is left untreated, after a year or so, the sore may heal, leaving a depressed pink or white scar which may cause considerable disfigurement, more especially when contraction of the scar-tissue occurs. The ulcerating form is always secondarily infected with pyogenic organisms, and in cases of long standing a streptothrix infection which eventually replaces the leishmania is not uncommon.

Other clinical types.—Other forms of open lesion are the eczematous and the verrucose; in the latter form, a cauliflower-like growth may involve a large area of the instep, for example.

There are many non-ulcerating forms, the commonest of which is the fleshy nodule that does not break down. There are also the keloid and the lupoid forms.

The lymph channels in the neighbourhood of the sore and the glands draining the area are often affected, but this involvement is almost always caused by the secondary invading organisms, although leishmaniae are occasionally found in the lymphatic glands. In some cases, subcutaneous nodules appear along the line of the lymph channel; these eventually break down and become separate ulcers (see figure 8, plate VIII).

The complications are those commonly associated with open ulcers. Lymphangitis has already been mentioned; less often phlebitis and erysipelas occur. When the scars contract they leave disfiguring deformities, *e.g.* ectropion.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

After considerable experience with this condition it is easy to make a diagnosis on clinical grounds alone with some degree of certainty, especially in the endemic areas. Otherwise the only satisfactory method of diagnosis is by examination of the lesions for leishmaniae. This is quite easily done in early lesions; it is more difficult in the open ulcers when secondary infection has led to the destruction of the parasites except in the deeper portions of the ulcer. After about a year it is seldom possible to demonstrate leishmaniae, and it is probable that they have died out and that the ulceration is maintained by the secondary organisms.

No parasites will be found in the pus taken from the centre of an ulcer, the secondary infecting organism alone being present. There are several ways in which the parasites can be demonstrated; if the lesion has not ulcerated or is in the first stages of ulceration, a simple method is first to sterilize the surface with alcohol and ether, then to wash it with sterile saline, to prick or scrape the spreading edge of the lesion so that it bleeds, to wipe away the first blood with a sterile swab, and to make a smear from the serous fluid which will subsequently come out. Or if this serous fluid is drawn up into a sterile pipette it can be placed into Nicolle, Novy and MacNeal (NNN) medium to obtain a culture of the organism.

The smear should be examined after staining by Leishman's or by Giemsa's method. When any surgical treatment is undertaken, a piece of the margin of the ulcer can be removed and a smear made from the cut edge of this piece, or a smear can be made from the deep scrapings of the ulcer after it has been cleaned and washed with saline.

Jessner and Amster obtained specific skin reactions in dogs and human beings by injection of a dilute blood-free vaccine of flagellates. Other antigenic substances have been used, but in view of the simplicity of the method of direct examination none of these can be recommended.

Differential diagnosis.—The condition must be differentiated from all other forms of skin nodule, boil, and ulcer. It is unnecessary to deal fully with all the non-specific boils and ulcers following an injury, or with syphilitic and varicose ulcers of the legs, but a few specific conditions, chiefly tropical or subtropical in their distribution, deserve special mention.

Each of these conditions has its characteristic appearance, which is distinct from that of the typical oriental sore, but all of them as well as oriental sore may vary from the typical. A knowledge of the geographical distribution of these diseases and of the recent movements of the patient is a most essential preliminary to accurate diagnosis; the final test is the demonstration of the specific organism, which in oriental sores of moderately short duration presents little difficulty.

Ulcus tropicum, the sloughing phagedænic ulcer of the tropics, is mainly confined to the legs and occurs in ill-nourished coolies. It usually begins with a water-blister or bleb, and sloughing is an earlier and more prominent feature. Scrapings from the base of this ulcer, after the slough has been cleaned away, will show the characteristic flora, a spirochæte and a fusiform bacillus.

Yaws is a disease of aboriginal races and occurs in all parts of the body, and the lesions are rarely single; the typical lesion is raised above the skin level, and, when the scab is removed, the characteristic 'raspberry' appearance is seen. *Treponema pertenuis* is found in the lesions, and the Wassermann reaction is positive.

Tuberculosis of the skin is not uncommon in the tropics, and, whether in the form of a tuberculide, which is more usual, or of an open ulcer, it may be mistaken for oriental sore; the extreme chronicity of these lesions and the characteristic appearance in the histological sections will settle the diagnosis.

The localized, raised and indurated lesions of **leprosy** may be mistaken for the non-ulcerating form of oriental sore; microscopical examination will settle the diagnosis. Leprotic ulcers will present less difficulty on account of their painlessness. In either case other manifestations of leprosy should be looked for but the presence of these does not necessarily exclude oriental sore.

Veld sore begins with a vesicle and is usually shallower than the oriental sore; it generally has an undermined edge and is very painful. *Corynebacterium diphtheriæ* is easily isolated in the early stages, but chronic sores of the two conditions present considerable difficulty.

A primary syphilitic sore on the lip is not at all unlike an oriental sore, nor is a tertiary gummatous ulcer. Microscopical examination will settle the diagnosis rapidly in the first case, and in the second a positive Wassermann reaction will be suggestive but not conclusive.

PREVENTION

General.—The general measures will include the avoidance of the source of infection and of the transmitting sand-fly.

All close association with infected human beings and infected dogs should be avoided. A dog-destruction campaign should be undertaken where these are suspected as carriers.

Sand-flies are very local in their habits, and it is often possible to get out of their range by moving a tent or hut only a few hundred yards: the banks of rivers and old brick or mud walls are their favourite habitats, but unfortunately sand-flies will also live in cracks in the ground. In special circumstances sand-fly control may be worth attempting (*see* p. 320).

Personal.—These will include the use of a sand-fly net (45/46 mesh), insect repellents (*see* p. 119), and possibly prophylactic inoculation.

The production of immunity by the injection of dead vaccine has not yet reached a satisfactory stage. Lawrow and Dubowskoj (1937) obtained very satisfactory results by the induction of single sores on the covered parts of the body by the injection of 0.1 to 0.2 c.cm. of living cultures: the sores appear in two to six months, increase in size for a time, and eventually heal in about twelve months' time.

TREATMENT

The cure of oriental sore is not so satisfactory as that of the visceral infection, kala-azar: this is evident from the large number of different forms of treatment that are advocated. No satisfactory comparative study has been undertaken since the newer forms of treatment were introduced, and most of the opinions expressed by different workers are based on clinical impressions.

The treatment may be (i) local or (ii) general. The local forms of treatment advocated can be considered under the headings (a) surgical treatment, (b) application of specific drugs, (c) physical measures, and (d) local injection of specific drugs. The general measures consist in the intravenous or intramuscular injection of various antimony preparations.

(i) **Local.**—(a) **Surgical.** In the pre-antimony days, surgical measures were mainly relied upon, *e.g.* vigorous scraping with a Volkmann spoon under an anæsthetic until all the friable tissue had been removed from the edges and base of the ulcer, which was then swabbed with pure liquefied phenol and dressed according to the particular choice of the surgeon. With the introduction of other forms of treatment, particularly those in which antimony was used, this rather crude surgical procedure fell temporarily into disfavour. However, as the newer forms of treatment have not lived up to their initial promise, there has been a tendency to return to this surgical treatment; the method of covering the wound directly with adhesive strapping and leaving it without further dressing for a week or more, after thorough scraping and treating with liquefied phenol under an anæsthetic, has given very satisfactory results and is probably the treatment of choice for the more advanced septic ulcers. For small ulcers direct application of liquefied phenol without previous scraping is said to be very satisfactory. Castor-oil dressings have given satisfactory results in some workers' experiences.

(b) **Application of specific drugs.**—Those recommended include potassium antimonyl tartrate ointment, 2 or even 4 per cent, powdered potassium permanganate, mercuric chloride, mercurous chloride, methylene blue ointment, and powdered sulphonamide; good results have been claimed with each of these drugs by certain workers, but none has proved generally satisfactory.

(c) **Physical measures.**—Solid carbon dioxide, diathermy, hot air, heliotherapy, x-ray, and radium have all been advocated as local applications. The first-named is the simplest and the most satisfactory. In

towns this is usually obtainable ready for application in the form of 'dry ice', otherwise a suitable stick can be prepared from a carbon-dioxide-gas cylinder. The dry ice is applied directly to the sore and held there for at least two minutes by the clock. There is a severe reaction with blistering, but when this has subsided the ulcer usually heals.

(d) **Local injections.**—Emetine hydrochloride has been used very often; 20 minims of a 5 per cent solution are injected into the margins of the sore. Mepacrine (atebrin) hydrochloride was suggested some years ago for local infiltration and according to some reports, a few of which are recent, is very satisfactory.

The local injection of **berberine sulphate** has in our hands produced some excellent results, and is, in the writer's opinion, the best of the drugs used for local infiltration; the drug appears to have a direct specific action on the parasites.

If the ulcer is septic, hot magnesium sulphate fomentations and frequent dressings should be used for a few days to make the wound as clean as possible. A 2 per cent solution of berberine sulphate is used; this is injected by means of a tuberculin syringe into the indurated area surrounding the ulcer; about six injections will be required for each ulcer in order to infiltrate the whole circumference of the ulcer, but 1 c.cm. of solution will usually be sufficient for an average-sized ulcer. There will usually be some inflammatory reaction, which should be allowed to subside before further injections are given; it will usually be possible to give the injections once a week. From three to six treatments will effect a cure. If there are multiple sores, not more than two or at the most three should be treated at one 'sitting', but treatments can be given daily, the ulcers being taken in turn. This treatment however cannot be recommended when there are more than half a dozen ulcers.

(ii) **General.**—The intravenous injection of tartar emetic solution was applied in the treatment of oriental sore immediately after it was introduced for the treatment of kala-azar. Good results are undoubtedly obtained in some cases, but the treatment is not without its dangers and unpleasant complications and cannot be recommended at the present day. When the pentavalent compounds of antimony were introduced, these were substituted for the antimony salts, and it was hoped that the results with these compounds would be as satisfactory as they were in kala-azar. The writer treated a number of cases with stibosan and, later, neostibosan. Cures were effected, but on the whole the progress was disappointingly slow. More recently we have used the aromatic trivalent antimony compounds, *e.g.* fouadin, with rather better results.

The dosage for neostibosan has already been given under the treatment of kala-azar (*see* p. 168). It is probably better to give the injections on alternate days rather than daily, and ten to twelve injections will usually be necessary.

Fouadin is supplied in ampoules as a 6.3 per cent solution: the starting dose is 1.5 c.cm. and the maximal single dose 5 c.cm. The injections are given intramuscularly on alternate days or three times a week, and eight to ten injections are usually sufficient.

It is too early to be dogmatic, but the evidence up to the present suggests that the aromatic diamidines, some of which are so successful in kala-azar, are quite useless in this condition.

To summarize, in those cases in which there are single or only a few early sores and non-ulcerating lesions, berberine sulphate is recommended; in cases with numerous small or moderate-sized lesions, foudadin or neostibosan injections should be given; and in all cases with extensive ulcers heavily infected with pyogenic organisms, recourse should be had to surgical treatment. Until the sore is obviously healing sulphonamide powder should be included in all dry dressings. A judicious combination of surgical treatment with antimony injections will produce the best results in cases with very numerous extensive ulcers.

PROGNOSIS

Under normal circumstances there should be no question of mortality from oriental sores, though no doubt many lives have been lost as an indirect result of these sores, especially when septic complications have followed. The two important points are the time taken in healing and the scarring left behind.

The course of an untreated sore is about a year; when eventually it heals, it always leaves a disfiguring scar.

Under efficient treatment simple sores will often heal in two to three weeks, but the average time taken for septic sores is probably at least two months.

In the case of a well-developed sore, even if efficient treatment is given, it is difficult to ensure healing without scarring, but the risk can be reduced considerably by suitable skin-grafting. A white scar will often become pigmented in the course of time. Early lesions that are treated by berberine sulphate injections usually heal completely, leaving no scar.

REFERENCES

- ACTON, H. W. (1919) .. A Study of the Distribution of Bagdad Boils on the Body made with a view to Discover the Transmitting Agent. *Indian J. Med. Res.*, **6**, 262.
- ADLER, S., and BER, M. (1941) .. The Transmission of *Leishmania tropica* by the Bite of *Phlebotomus papatasi*. *Indian J. Med. Res.*, **29**, 803.
- ADLER, S., and THEODOR, O. (1926) .. Further Observations on the Transmission of Cutaneous Leishmaniasis to Man from *Phlebotomus papatasi*. *Ann. Trop. Med. and Parasit.*, **20**, 175.
- AGRONICK, M. A. (1925) .. On the Propagation, Pathogenesis and Treatment of the Oriental Sore. *Russian J. Trop. Med.*, Nos. 1-2-3, p. 74. (Abstract—*Trop. Dis. Bull.*, 1926, **23**, 584.)
- Idem* (1927) .. Epidemiology and Symptomatology of Oriental Sore. *Dermat. Woch.*, **84**, 261. (Abstract—*Trop. Dis. Bull.*, **24**, 641.)
- BOBOWSKY (1898) .. Uber das Sartengeschwür. *Wojennomedizinsky J.*, November, S 925.
- CARTON, M., and BACQUE, M. (1921). Notes sur le Clou de Biskra chez les Tirailleurs Sénégalais à Biskra (Algérie). *Ann. Med. Pharm. Coloniales*, **19**, 303.
- CUNNINGHAM, D. D. (1885) .. On the presence of peculiar parasitic organisms in the tissue of a specimen of Delhi Boil. *Scientific Memoirs by Medical Officers of the Army of India*, Pt. I, 1884, p. 21. Supdt., Govt. Printing, India, Calcutta.

- DOSTROWSKY, A. (1926) .. A Study of Cutaneous Leishmaniasis in Palestine. *Ann. Trop. Med. and Parasit.*, **20**, 385.
- GOODALL, J. (1937) .. Clinical Study of Sixty-three Cases of Oriental Sore. *Indian Med. Gaz.*, **72**, 3.
- JESSNER, M., and AMSTER, S. (1925). Leishmanivaksine—Leishmaniinreaktion. *Deut. Med. Woch.*, **51**, 784.
- LAWROW, A. P., and DUBOWSKOJ, P. A. (1937). Uber Schutzimpfungen gegen Hautleishmaniose. *Arch. Schiffs- u. Trop.-Hyg.*, **41**, 374.
- MARZINOWSKY, E. J., and BOGROW, S. L. (1904). Zur Aetiologie der Orientbeule (bouton d'Orient). *Virchows Archiv. Pathologische Anatomie u. Physiologie*, **178**, 112.
- MARZINOWSKY, E. I., and SCHOUEN-KOFF, A. I. (1924). Immunity in Oriental Sore. *Russian J. Trop. Med.*, No. 2, p. 17. (Abstract—*Trop. Dis. Bull.*, **21**, 726.)
- NAPIER, L. E. (1938) .. Oriental Sore. *British Encyclopædia of Medical Practice*, **7**, 665. Butterworth and Co., Ltd., London.
- NAPIER, L. E., and HALDER, K. C. (1936). The Incubation Period of Oriental Sore. *Indian Med. Gaz.*, **71**, 723.
- NICOLLE, C., and SICRE, A. (1908) .. Recherches sur le bouton d'Orient. *Arch. Inst. Pasteur, Tunis*, **3**, 117.
- PATTON, W. S. (1922) .. Some Reflections on the Kala-azar and Oriental Sore Problems. *Indian J. Med. Res.*, **9**, 496.
- SERGEANT, ED. ET ET., PARROT, L., DONATIEN, A., and BEGUET, M. (1921). Transmission du clou de Biskra par le phlébotome (*Phlebotomus papatasi*, Scop). *Compt. Rend. Acad. Sci.*, **173**, 1030. (Abstract—*Trop. Dis. Bull.*, 1922, **19**, 315.)
- SHAH, M. H. (1941) .. Report on the Epidemic of Oriental Sore in Delhi. *Indian Med. Gaz.*, **76**, 449.
- WENYON, C. M. (1911) .. Note on the Occurrence of Herpetomonas in the Phlebotomus of Aleppo. *J. London School Trop. Med.*, **1**, 98.
- Idem* (1912) .. Some Remarks on the Successful Inoculation of *Leishmania tropica* to Man. *J. London School Trop. Med.*, **1**, 224.
- WRIGHT, J. H. (1903) .. Protozoa in a Case of Tropical Ulcer ('Delhi Sore'). *J. Med. Res.*, **10**, 472.
- YAKIMOFF, W. L., and SCHOCKOV, N. F. (1915). Leishmaniose cutanée (bouton d'Orient), au Turkestan russe. *Compt. Rend. Soc. Biol.*, **78**, 107.

SOUTH AMERICAN MUCO-CUTANEOUS LEISHMANIASIS

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Definition.—Muco-cutaneous leishmaniasis or espundia (known also as uta, Bauru ulcer, forest yaws, and by many other local names) is a specific granuloma of the skin, that usually ulcerates and forms a chronic ulcer, on various, mainly the exposed, parts of the body; in a variable percentage of cases, secondary ulcerative lesions occur in the mucosa of the mouth and upper respiratory tract. The disease is almost entirely confined to Central and South America; it is caused by a protozoon, *Leishmania brasiliensis*, which is transmitted from host to host by sand-flies of the genus *Phlebotomus*.

Historical.—The disease has undoubtedly existed in America for some considerable time. Certain observers consider that the drawings on the Inca pottery, on which men with typical lesions are shown, are evidence of the existence of the disease before the discovery of America (da Matta, 1918); on the other hand, it has been claimed that other infections common in South America cause similar scars, and the suggestion has been made that the disease was imported from the Old World.

Lindenberg (1909) and Carini and Paranhos (1909) were the first observers to establish the ætiological relationship between this disease in Brazil and oriental sore, by finding leishmania in the lesions of the former.

EPIDEMIOLOGY

Geographical distribution.—The disease is endemic in Central and South America. It has been reported as far north as Yucatan in Mexico

and as far south as Buenos Aires, but the more highly endemic areas are north of the Tropic of Capricorn. The disease has been studied most in Brazil and Peru, but it is also reported from Columbia, Venezuela, British, Dutch and French Guiana, Chile, Bolivia, Paraguay, Uruguay and Argentina. It is a serious public health problem in rural districts of Minas Geraes in Brazil (Orsini, 1940).

In most of the northern endemic areas, the secondary mucosal lesions are rare, and it has been definitely stated that in some places they do not occur; as one travels further south, however, the mucosal lesions appear to increase in frequency, and in some places, in as many as 20 per cent of cases, cutaneous lesions are followed eventually by mucosal lesions.

Isolated instances of mucosal lesions following what appeared to be oriental sores have been reported from Europe and Africa, and in the Sudan, Kirk, who has observed a number of different cutaneous manifestations of leishmania infection, has described some that are suggestive of espundia, though no parasitological studies have been carried out to confirm or otherwise the identity of the causal organism with *L. brasiliensis*.

Local distribution and altitude.—The disease is contracted mainly in forest regions, and the most serious epidemics have occurred amongst workers in virgin forest; marshy areas seem to favour dissemination of the infection. In Mexico the disease occurs amongst chicle-gum gatherers (Inchaustegui, 1918). Burga (1926) says that in Amazonia it is limited to an area with an altitude not more than 2,000 feet above sea level, which area is nevertheless characterized by a temperate climate.

Seasonal incidence.—The infection appears to be definitely seasonal, and in Sao Paulo the ulcers appear mainly in late summer and autumn months (da Silveira, 1920), but Cerquiera and de Vasconcellos (1923) refer to an epidemic in Rio de Janeiro occurring in May to August.

Age, sex, and race.—Although persons of all ages from infants at the breast (Migone, 1915), of all races, and of both sexes are susceptible, the disease attacks mostly male adults—over 90 per cent of patients are male adults according to Villela (1939)—probably on account of the fact that they are most frequently exposed to infection.

ÆTIOLOGY

Historical.—Lindenberg (1909) and Carini and Paranhos (1909) first reported the findings of the parasite in the ulcerative skin lesions, and Splendore (1911) found it in the mucosal lesions. Vianna (1911) gave the causal organism the name *Leishmania brasiliensis*.

The causal organism.—*Leishmania brasiliensis* is morphologically indistinguishable from *L. donovani* and *L. tropica*. The cultural forms are also identical, but serologically these three species can be distinguished from one another (Noguchi, 1924). (For morphology and staining see KALA-AZAR.)

Distribution of the parasite.—The parasites are found readily in the cutaneous lesions, in the early stages of the infection, but later they become scanty. They can also be found in the lymph nodes on the course of the lymphatics that drain the site of the ulcer. Parasites must eventually reach the blood, as their subsequent distribution in the mucous membranes can be achieved only through the blood stream; neither direct extension nor lymphatic spread can account for these lesions. *Leishmaniae* can sometimes be found in the intact mucous membrane in cases with cutaneous lesions only, but are often difficult to demonstrate when there is ulceration and secondary infection.

In animals, Brumpt and Pedroso (1913) found the parasite in lesions on the noses of dogs. Mazza (1927) reported infection in a horse.

In the laboratory, cats, dogs, monkeys, guinea-pigs, and mice have been infected.

Transmission.—The parasite is almost certainly transmitted to man by a species of *Phlebotomus*. *Phlebotomus intermedius* is under suspicion.

PATHOLOGY

There is no essential difference between the cutaneous lesions in this condition and those in *Leishmania tropica* infection. The histopathology of the disease in the mucosa has been studied by Klotz and Lindenberg (1923). In the earliest stage, there is oedema of the submucosa, and perivascular lymphocytic infiltration; in the inflammatory focus thus formed, although the lymphocytes predominate, there are a few endothelial cells, some of which may contain leishmanix. The epithelium at this stage is intact.

The infected lymph nodes show macrophage infiltration, but the picture is usually complicated by secondary infection. Later, there is some fibrosis.

In the second phase of the infection, the mucosa becomes swollen and there is desquamation of the epithelium over the infected focus; the ulceration of the epithelium continues independently of the pathological process in the deeper structures and eventually there appears a definite area of superficial necrosis, covered by a fibrinous exudate. Meanwhile the perivascular infiltration becomes more extensive and diffuse, involving the surrounding lymphatics, and a change takes place in the nature of the cell exudate; there is a definite increase in the number of plasma and endothelial cells, and as the process continues the endothelial proliferation becomes a more and more marked feature; eventually numerous multinucleate cells containing large numbers of leishmanix appear.

Finally, the endothelial proliferation progresses and the cells show a tendency to form groups, and eventually nodules, along the course of the small blood vessels. As the nodules form, the reaction in the surrounding tissue subsides and the normal structure of this tissue reappears. These granulomatous nodules eventually go on to necrosis and fibrosis; when they are near the surface, secondary infection occurs, and endarteritis leading to complete occlusion of the vessels follows.

SYMPTOMATOLOGY

There are two phases of the infection, the primary phase of cutaneous ulceration, and the secondary phase of infection of the mucosa of the buccal cavity and upper respiratory tract.

Though many patients first come under observation with mucosal lesions, they usually give a history of primary cutaneous lesions, but there are instances when this history cannot be obtained (Villela, 1939).

Cutaneous lesions.—In most cases the incubation period appears to be from 2 to 3 months.

In general, the lesions can be divided into two main types, the ulcerating and the non-ulcerating. The latter may be subdivided into the hypertrophic variety in which either a simple papillomatous or a cauliflower-like growth is formed, and the atrophic variety in which there is a red plaque with raised edges.

Lesions occur almost always on uncovered parts of the body, on the ears, face, neck, arms, wrists, legs and ankles; they are usually multiple.

The ulcerating type commences as a small red itching papule or as a localized papular erythema. The papules go on to pustule formation, break down and form small ulcers. The ulcer is surrounded by an oedematous area which eventually becomes necrosed, until in some instances an ulcer of 9 or 10 centimetres diameter is formed. The ulcers are usually round, but may be asymmetrical. The edges are at first undermined, but later become clean-cut, slightly raised and surrounded by a narrow area of induration. There is a purulent exudate. In many instances there is lymphatic involvement following on local infiltration around the ulcers; there may be subcutaneous nodule formation along the course of the lymphatics, and the glands become enlarged and painful; this glandular enlargement is not entirely due to septic invasion of the ulcer, since leishmaniae can be recovered from the glands. The glands often fail to regain their natural size after the local condition is cured.

The papillomatous type commences in much the same way, but the red papule, instead of becoming a pustule, increases in size and exudes a serous fluid which may form a crust; under this crust, which soon scales off, lies the thin but intact epithelium. The non-ulcerating type may eventually, after many months or even years, break down and become an ulcer.

The mucosal lesions.—As already stated, the frequency of the occurrence of the mucosal lesions varies in the different areas of activity of the disease. In the northern areas, the secondary mucosal lesions are rare, but in the southern areas, São Paulo for example, Klotz and Lindenberg (1923) report that from 15 per cent to 20 per cent of those patients who have had cutaneous lesions for more than two years suffer from mucosal lesions, and Villela, Pestana and Pessoa (1939) that in practically all untreated cases of cutaneous lesion, there is infection of the nasal mucosa which may or may not break down. In 12 cases without clinical symptoms referable to the nasal mucosa, 5 showed small lesions, and in the rest, smears made from the mucosa showed leishmaniae.

When they occur, the mucosal lesions usually appear 6 to 18 months after the cutaneous lesions, but in some cases the onset of the nasal lesions has been delayed for as long as 15 years. They usually commence as an oedematous swelling of the mucous membrane of the nose, followed by the formation of small raised granular ulcers; these enlarge and spread, with the formation of granulation tissue. Villela (*loc. cit.*) reports that 78 per cent of the lesions are in the nose. All the soft parts of the nose, mouth and pharynx may be involved and destroyed. The bones and the tongue are not, however, attacked. The patient, when untreated, usually dies from septic absorption, pneumonia, or starvation from blockage of the passages.

DIAGNOSIS

This does not usually present much difficulty when there are early cutaneous lesions; the indurated edge of the ulcer is pricked and a smear made from the exudate will usually show leishmaniae (*see ORIENTAL SORE*). In older sores it may be difficult to find them.

In cases with mucosal lesions, it is usually possible to find the leishmania by scratching the intact part of the mucous membrane of the nose and making a smear from the exudate. Smears from the lesions themselves will seldom show leishmaniae.

The intradermal test of Montenegro is a valuable specific test. This is done by injecting intradermally 0.1 c.cm. of a suspension of a culture of *Leishmania brasiliensis* in 0.4 per cent phenol. Within 48 hours there is a sharp local reaction which persists up to 72 hours. The test first becomes positive after about a month and continues to be positive as long as the lesions remain.

Costa (1916) described certain ocular complications which have occurred in this condition, a new growth in the centre of the cornea, and lesions in the lower eyelid accompanied by opacity of the vitreous.

The condition has to be differentiated from leprosy, framboesia, blastomycosis and syphilis; it differs from the last named in that, in the leishmania infection, bones are not attacked and, in syphilis, the ulceration does not usually spread beyond the muco-cutaneous margin.

PREVENTION

The only absolute means of control is by anti-sand-fly measures, but little is known about the bionomics of sand-flies.

Ointments and repellents of various kinds will prevent sand-fly bites, but the indigenous inhabitants of the areas where the infection occurs could scarcely use these throughout the transmitting season.

The thorough treatment of all cutaneous lesions must be looked upon as the only means of preventing the more serious mucosal lesions that can be applied at present with much hope of success.

TREATMENT

This should be both general and local. The local treatment recommended for oriental sore (*q. v.*) can be applied for the cutaneous lesions in this infection, but general treatment must also be applied to prevent the later development of mucosal lesions.

Vianna and Marchado (1913) used potassium antimonyl tartrate by the intravenous route in this disease, and thereby initiated a new era in the treatment of leishmaniasis. Antimony has been the mainstay in the treatment ever since.

The new antimony compounds have been used more recently, and fouadin (sodium antimony pyrocatechin sulphonate) has been one of the most successful. It is given in a 6.3 per cent (isotonic) solution, in doses of 1.5 c.cm. increasing to 5.0 c.cm., intramuscularly, daily at first and then on alternate days, up to 15 to 20 injections.

Arsphenamine preparations are sometimes used for the cutaneous lesions, but, whilst curing these (after 3 or 4 injections), they leave the mucous membrane infections intact; nasal ulceration usually follows eventually, and in the end antimony has to be resorted to.

Recently, it has been claimed that atabrin injected locally and given by mouth at the same time is a specific for the cutaneous lesions, and yatren given intravenously combined with fouadin is said to accelerate the cure of the mucosal lesions.

For local application to the mucosal lesions, a bicarbonate of soda gargle for the throat and nose, followed by a wash of 0.1 per cent solution of tartar emetic is said to be useful. Another method is spraying with a 2 per cent solution of tartar emetic after anæsthetizing with a spray of 1 per cent cocaine plus 1 per cent phenol.

REFERENCES

- BRUMPT, E., and PEDROSO, A. (1913). Recherches Epidémiologiques sur la Leishmaniose Forestière Américaine dans l'Etat de São-Paulo (Brésil). *Bull. Soc. Path. Exot.*, **6**, 752.
- BURGA, B. (1926) Distribución Geográfica de las Leishmaniasis en el Departamento de Amazonas. *Cronica Med. Lima*, **43**, 169. (Abstract—*Trop. Dis. Bull.*, 1927, **24**, 642.)
- CARINI and PARANHOS, U. (1909) .. Identification de l' 'Ulcera de Bauru' avec le Bouton d'Orient. *Bull. Soc. Path. Exot.*, **2**, 255.
- CERQUIERA, A. DE C., and DE VASCON-CELLOS, A. (1923). La Leishmaniose a Rio de Janeiro. *Bull. Office Internat. d' Hyg. Publique*, **15**, 123.
- COSTA, P. (1916) Nota Preliminar Sobre lesões Oculares da Leishmaniose. *Gaz. Med. Bahia*, **47**, 496. (Abstract—*Trop. Dis. Bull.*, 1917, **10**, 65.)
- INCHAUSTEGUI, A. (1918) .. De la Leishmaniosis Americana y de la Ulcera de los Chicleros en Mexico. *Thèse Mexico*, p. 100. (Abstract—*Bull. Inst. Pasteur*, 1920, **18**, 576.)
- KIRK, R. (1942) Studies in Leishmaniasis in the Anglo-Egyptian Sudan. V. Cutaneous and Muco-cutaneous *Leishmaniasis*. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **36**, 257.
- KLOTZ, O., and LINDENBERG, H. (1923). The Pathology of Leishmaniasis of the Nose. *Amer. J. Trop. Med.*, **3**, 117.
- LINDENBERG, A. (1909) .. L'ulcère de Bauru ou le Bouton d'Orient au Brésil. *Bull. Soc. Path. Exot.*, **2**, 252.
- DA MATTA, A. (1918) Notas para a Historia das Leishmanioses da pelle e das Mucosas. *Amazonas Medico*, **1**, 11.
- MAZZA, S. (1927) *Bol. Inst. Clin. quir. B. Aires*, **3**, 472.
- MIGONE, L. E. (1915) .. Buba, or *Leishmaniasis Americana*, in Paraguay. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **8**, 219.
- NOGUCHI, H. (1924) .. Action of certain biological, chemical, and physical agents upon cultures of *Leishmania*; some observations on plant and insect Herpetomonads. *Proc. Internat. Conference on Health Problems in Trop. America*, p. 455. United Fruit Co., Boston, Mass.
- ORSINI, O. (1940) Leishmaniose em Minas Geraes. *Brasil-Medico*, **54**, 762. (Abstract—*Trop. Dis. Bull.*, 1941, **38**, 576.)
- DA SILVEIRA, R. (1920) .. Frequencia e Distribuicao da Leishmaniose em S. Paulo. *Brasil Medico*, **34**, 200. (Abstract—*Trop. Dis. Bull.*, **16**, 458.)
- SPLENDORE, A. (1911) .. Buba-Btastomicosi-Leishmaniosi (Nota sopra alcune affezioni Framboesiche Osservate nel Brasile). *Policlinico*, 18C.
- VIANNA, G. (1911) Sobre una nova Especie de *Leishmania*. *Brasil Med.*, No. 41.
- VIANNA and MARCHADO (1913) .. Reports of two cases of Muco-cutaneous *Leishmaniasis* treated with Intravenous Tartar Emetic. *Bol. Soc. Brasileira Dermat.*, **2**, 17.
- VILLELA, F. (1939) Dados Estatísticos Sobre a Leishmaniose das Mucosas em Aracatuba, S. Paulo. *Folha Med.*, **20**, 243. (Abstract—*Trop. Dis. Bull.*, 1940, **37**, 352.)
- VILLELA, F., PESTANA, B. R., and PESSOA, S. B. (1939). Presença da '*Leishmania brasiliensis*' na Mucosa Nasal sem Lesão Aparente, em Casos Recentes de Leishmaniose Cutanea. *Hospital Rio de Janeiro*, **16**, 953. (Abstract—*Trop. Dis. Bull.*, 1940, **37**, 353.)

SLEEPING SICKNESS, OR AFRICAN TRYPANOSOMIASIS

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Definition.—Sleeping sickness is a specific disease confined to tropical Africa, characterized in its early stages by fever, glandular enlargement, and anæmia, and, in its later stages, by progressive involvement of the central nervous system; it is caused by *Trypanosoma gambiense*, or *Trypanosoma rhodesiense*, protozoa of the family Trypanosomidæ, which are transmitted to man by tsetse flies, flies of the genus *Glossina*.

Historical.—Since the beginning of the 18th century there have been sporadic references to a mysterious lethargy that fell upon the natives of certain parts of equatorial Africa, but with the further development of the slave trade and its penetration into new areas, the commercial implications became apparent, and the casual interest in this disease gave way to a more purposeful one. Slaves taken to the West Indies developed the disease shortly after arrival, and, though the disease did not spread there, the slave became useless as a slave, and even if he did not die immediately he was a dead loss to the trader. The condition was attributed to homesickness, but nevertheless it was observed that slaves from certain areas were more prone to 'brooding' than those from others. Further, the slave trade in Africa itself led to the introduction of the disease into new areas where it spread to the local population and thereby disturbed the humanitarian and embarrassed the commercial interests of the foreign intruders. During the first half of the 19th century, there was a steadily increasing number of references to *la maladie de sommeil* in medical literature, but no material progress in its elucidation was made.

Quite independently, but again mainly because of its commercial implications, attention was directed to nagana, a disease of domestic bovines and equines, which interfered with transport and agricultural development in tropical Africa. It was believed as early as the middle of the century that the tsetse fly was the cause of this disease (Livingstone, 1857), and a definite 'fly belt' was recognized. Bruce investigated nagana; in 1895 he found trypanosomes in the blood of cattle dying of this disease and proved that it was the causal organism. (In 1880, Evans had demonstrated trypanosomes as the cause of surra in horses in Madras.) He demonstrated that the infection was transmitted by glossina, and that wild game were the reservoirs of infection but did not themselves suffer any disease from the presence of the parasites in their blood.

The first recorded finding of a trypanosome in the human blood was that of Nepveu, who, while looking for malaria parasites, found trypanosomes in the blood of a man in Algiers in 1890, but he did not recognize the significance of the observation. Forde (1901) was the first to observe

a trypanosome in a case that in retrospect can be recognized clinically as sleeping sickness, but he did not know what the 'worm-like' body was. This same patient returned from Gambia to England, and Dutton again found the parasite in his blood, recognized it as a trypanosome, and named it *Trypanosoma gambiense*.

The first Sleeping Sickness Commission (Royal Society) went out to Uganda in 1902, and Castellani, one of its members, discovered trypanosomes in the cerebrospinal fluid of patients suffering from sleeping sickness, but was more attracted by some streptococci that he also found. The second Royal Society Sleeping Sickness Commission operated from 1903 to 1906 with Bruce at its head. Not unnaturally Bruce, remembering his experience with nagana and the findings of Forde and Dutton in the blood and of Castellani in the cerebrospinal fluid, pieced together the whole story, but probably no other medical investigation has been carried through so methodically and with such painstaking restraint as the work of this commission which proved that sleeping sickness was due to *Trypanosoma gambiense* and that it was transmitted from man to man by the tsetse fly, *Glossina palpalis*.

Until its ætiology had been thus established, sleeping sickness was not recognized as a single syndrome, though the natives of Africa themselves and the early clinical observers had noticed that those who had cervical glandular enlargements were liable to the *la maladie de sommeil* at a later date.

In 1910, Stephens and Fantham found trypanosomes in the blood of a man who had come from Rhodesia; they considered that it differed from *T. gambiense* and named it *Trypanosoma rhodesiense*. In the following year, Kinghorn and Yorke showed that this trypanosome was transmitted by another tsetse, *Glossina morsitans*. It was soon recognized that the geographical distribution of the disease caused by these two trypanosomes was quite distinct and that, though similar, they were clinically distinguishable, and later it was shown that they responded to treatment very differently.

Subsequent investigations have shown that certain other species of *Glossina* are capable of transmitting the infection, but only two of these are of any importance, namely *G. tachinoides*, as a transmitter of *T. gambiense* and *G. swynnertoni* as a transmitter of *T. rhodesiense*.

In his work on nagana, Bruce visualized only the direct transmission of the infection from animal to animal by the contamination of the proboscis of the tsetse, and later, in his work on human trypanosomiasis, he definitely stated that the fly was capable of transmitting the infection only for 48 hours; but later it was shown by numerous workers, led by Kleine (1909), that there was also cyclical transmission, that is, the trypanosome underwent a cycle of development in the fly before it was transmitted; Bruce (1910) at first placed the time interval as five weeks.

For the last thirty years much of the work has been of an epidemiological nature, and that of Duke, Swynnerton and others has centred round the problem of whether or not *T. brucei*, which infects cattle and of which wild game act as a reservoir, is identical with *T. rhodesiense*. The problem has not yet been solved, but it is generally believed that at least they have a common origin, and the issue has now tended to become—under what conditions does the trypanosome found in cattle acquire the ability to infect man, and, conversely—when passaged through bovines, under what conditions will the trypanosome causing the Rhodesian type of sleeping sickness lose its properties as a human pathogen? The recent investigations

of Corson and others between 1930 and 1938 suggest that in both cases the trypanosomes show a considerable degree of stability (Corson, 1939).

ETIOLOGY

The causal organism.—As indicated above, there are two species of trypanosome, *Trypanosoma gambiense* and *Trypanosoma rhodesiense*, that cause the two forms of sleeping sickness; they are protozoa of the class Mastigophora, family Trypanosomidae.

Morphology and staining.—These two trypanosomes are morphologically indistinguishable in the peripheral blood of man. In the fresh specimen of peripheral blood, the trypanosome is a rapidly moving spindle-shaped body with an undulating membrane and flagellum; it can be seen easily as it disturbs the red cells, but, for the study of further details of its structure, the unstained specimen is unsatisfactory.

In the blood smear stained by Leishman's or Giemsa's method, the trypanosome is seen as a spindle-shaped body 14 to 32 μ in length and 1.5 to 3.5 μ in breadth, with a parabasal body and a blepharoplast at the posterior end; from this a flagellum arises, passes forward along the whole length of the body to which it is attached by an undulating membrane, and extends for about one-quarter of its length beyond the anterior end of the body. About the middle of the body is an oval-shaped nucleus with a centrally-placed karyosome (seen only in a hæmatoxylin-stained specimen) which occupies about two-thirds of the breadth of the cytoplasm. The cytoplasm stains a light blue; it contains dark-blue granules and sometimes vacuoles. The trophonucleus stains a reddish purple, and the parabasal body and blepharoplast usually appear as one dark-red mass. The undulating membrane is a transparent pale-violet membrane.

There are two distinct forms of trypanosomes, the thin slender forms that are the usual ones seen in the peripheral blood, and the broad stumpy ones less frequently encountered; in the latter, the flagellum ends with the undulating membrane at the anterior end of the body of the parasite, and there is no free flagellum. In both types of infection, these two forms maintain about the same proportions, the slender form always predominating, and intermediate forms are found.

The parasite multiplies by binary longitudinal division of the trypanosome forms; all stages of division may be seen in the peripheral blood.

In the cerebrospinal fluid the same forms will be seen, but they are more pleomorphic, and involution forms are frequently seen.

Crithidial forms, in which the blepharoplast is anterior to the nucleus, occur at certain stages in the insect vector (*vide infra*), but are not found in man.

Though the two species of trypanosome are identical in the blood of man, when the infection is transferred to a laboratory animal, they exhibit certain differences, and in the case of *rhodesiense* infection a percentage, often about 5 per cent, of the trypanosomes are posterior-nuclear forms, in which the nucleus is near or actually at the posterior end, in which case the blepharoplast is necessarily anterior to it.

Culture.—Trypanosomes will survive for many weeks in NNN culture medium (*see* p. 161), but there is little multiplication, and subcultures cannot be obtained.

Distribution in the body.—Trypanosomes are found in the blood, lymph glands and lymph vessels in the early stages of the disease, and in

the cerebrospinal fluid in the later stages. The parasites never invade the cells, but are found in the connective tissue spaces of many organs in the intra-cellular spaces of the brain, and in the reticular tissue of the spleen and lymph glands.

Pathogenesis in animals.—Both trypanosomes will infect laboratory animals, rats, guinea-pigs, and rabbits, but *rhodesiense* produces a much more virulent infection in these animals; further, this latter parasite gives rise to the posterior-nuclear forms referred to above, which are only very rarely found when a *gambiense* infection is transmitted to a laboratory animal.

The infection can be transmitted to many species of wild antelope, but only one species has been found infected with what appeared to be *T. gambiense*, in nature; on the other hand, *T. rhodesiense* is believed by some workers to be identical with *T. brucei* which is a common natural infection in wild game, and which, when transmitted to domestic equines and bovines, causes nagana (*vide supra et infra*).

In the tsetse fly, trypanosomes will be found in the gut, mouth parts, and salivary glands, in all of which sites they multiply (*vide infra*).

Strains.—As in many other infections, there is evidence that, in addition to the differences in species, there are a number of different strains of the causal organism, which vary in their virulence to man and animals, and in their susceptibility to drugs. It seems possible that many, if not all, the puzzling variations in the pathogenicity of trypanosomes in different animal species, and in drug-resistance might be explainable on a theory of strain selectivity of vectors, hosts and drugs.

Immunity.—There is evidence of both natural and acquired immunity to trypanosome infection.

Normally, man is resistant to infection with *T. brucei*, less so to infection with *T. rhodesiense*, but susceptible to infection with *T. gambiense*. Yorke and his co-workers consider that there is evidence to suggest that in the presence of special conditions, *e.g.* some other infection or dietary deficiencies, the trypanocidal action of the blood of man is destroyed, and that he then becomes susceptible to infection with *T. brucei*, which once established acquires a degree of resistance to the trypanocidal action of human blood, is capable of establishing itself in a normal individual, and becomes what we know as *T. rhodesiense*; finally, as this trypanosome is transmitted rapidly from man to man by the tsetse fly, its potentialities for infecting man become still more fixed, it loses its pathogenicity for cattle though it still infects them, and becomes *T. gambiense*. There are still many gaps in this attractive theory.

On the whole, the African native shows a greater degree of immunity than the European intruder; in the latter, the disease tends to run a more acute course.

Transmission.—This is effected by the agency of certain species of *Glossina*. This may be (i) direct or (ii) cyclical.

Direct.—It has been shown that when a fly that is feeding on an infected animal is interrupted, and then immediately allowed to feed on another uninfected animal, the infection will be transferred to the second animal, presumably by the contaminated mouth parts of the fly; there is evidence that this occurs in nature and that, during epidemic periods in particular, infection is transferred from man to man by this means, but it is also certain that the cyclical method of transmission is the usual one. Certain *Stomoxys* species are capable of transmitting the infection directly.

Cyclical.—The fly takes the infected blood containing trypanosomes (figure 45, 1) into its mid-gut; there the blood is digested, but trypanosomes (1a) multiply and undergo a slight change in morphology, becoming larger and broader; later, long slender forms appear (2); these pass round the lower free end of the peritrophic membrane and occupy the space between this and the epithelial lining of the gut wall, where they continue to multiply for some days; in this extra-peritrophic space they move anteriorly and reach the level of the proventriculus, where they penetrate the peritrophic membrane and reach the lumen of the proventriculus (2a). At this stage the trypanosomes are now all long slender forms; they continue to multiply, and, still moving forwards, they reach the opening of the salivary duct (2b) and eventually the salivary glands. In the salivary glands they continue to multiply, but undergo a further change of morphology, becoming first crithidial (3) and then 'metacyclic' (4) forms, short forms that are very similar to the short forms seen in the peripheral blood. The metacyclic forms are injected with the salivary gland secretion (4a) into the wound made by the tsetse fly's proboscis.

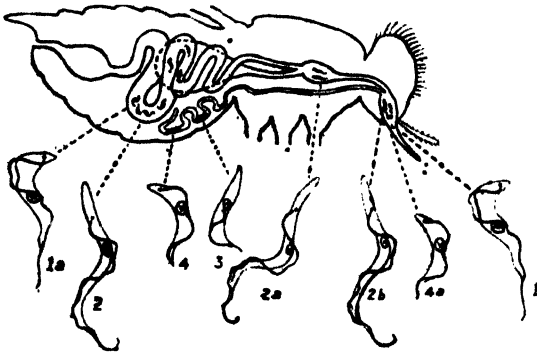


Figure 45: Diagrammatic outline showing position of different forms of trypanosome in the tsetse fly.

1. Trypanosome form, as found in the peripheral blood, in the hypopharynx; entering.
- 1a. Same form in the mid-gut.
2. Long slender form in the mid-gut.
- 2a. Same form in the proventriculus.
- 2b. Same form in the hypopharynx; on the way to the salivary glands.
3. Crithidial form in the salivary glands.
4. Metacyclic form in the salivary gland.
- 4a. Same form in the hypopharynx; on the way out.

The trypanosome loses its powers of infecting vertebrates soon after it reaches the mid-gut of the fly, but when it reaches the metacyclic stage it again becomes infective; the whole cycle takes from 10 to 25 days according to the circumstances, temperature (optimum 75° to 85°F.) being the most important factor.

In only a proportion of flies—even of the recognized transmitting species—that feed on infected blood do the trypanosomes complete this cycle, but, when once infected, a tsetse fly remains infected indefinitely, the salivary infection being periodically replenished from the extra-peritrophic space. Newly hatched flies are more readily infected than older ones that have already taken a number of blood meals.

The infection is not transmitted hereditarily in the tsetse.

Other possible means of transmission.—A few cases of congenital infection have been reported, and transmission is also said to occur during coitus.

The tsetse-fly vectors.—There are four species of *Glossina* concerned in the transmission of sleeping sickness, *G. palpalis* and *G. tachinoides*, *G. morsitans* and *G. swynnertoni*; in nature the first two transmit the *gambiense* and the latter two the *rhodesiense* infections, though in the laboratory many other species have been shown to be capable of transmitting both infections.

Flies of the genus *Glossina* (family Muscidae) are larger than *Stomoxys*, and have a similar type of proboscis, but a more hairy arista. The characteristic posture of the fly at rest is with wings folded scissor-wise; the wings show distinctive venation. They have a short stout proboscis, thick palpi with broad channels on their inner surfaces in which the proboscis lies (see figure 46 and plate I).

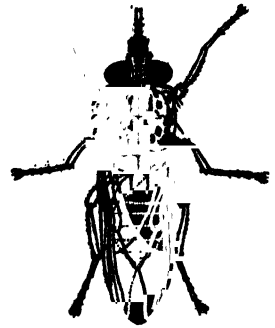


Figure 46 : The tsetse fly $\times 3$.

A diagrammatic representation of the internal anatomy of the tsetse is shown in figure 45. In figure 47, the relative position of the peritrophic membrane is shown. This membrane is secreted by the epithelium of the mid-gut and is designed to protect the delicate epithelium from the direct action of the ingested meal. It is a sleeve-like structure with a lower end free and the upper end attached at the level of the proventriculus. It might be compared to a coat sleeve lining that only reaches to the elbow where it ends free, the upper end being sewn to the sleeve proper at the shoulder seam.



Figure 47 : Diagrammatic outline of mid-gut of tsetse fly.

The female fly does not lay eggs but gives birth periodically (about once a fortnight) to a larva (in girth nearly as big as the female itself) which it drops in a shady spot usually not far from water; this larva crawls into a place of safety and

immediately pupates. The pupa hatches into an adult after an interval varying from three weeks (at 85°F.) to a month or two according to the environmental conditions.

Both male and female tsetse flies feed on vertebrate blood, and flies of either sex are capable of transmitting trypanosomes. They feed almost exclusively during the day.

Reservoirs of infection.—The rôle of wild game is a controversial subject. As far as the Gambian disease is concerned, it is generally believed that man is the sole source of infection and that game do not play an important part in the ætiology of this infection; many species, of wild game, as well as domestic bovines and pigs, are potential carriers, and one species of antelope has been found infected in nature by a trypanosome that appeared to be *T. gambiense*.

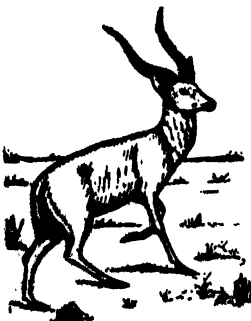


Figure 48

It is however fairly certain that wild game are the main reservoirs of infection of the Rhodesian type of sleeping sickness, for the disease occurs mainly amongst those who come in close contact with wild game, is usually sporadic, and only in special circumstances becomes epidemic. This whole problem is mixed up with that of the identity, or otherwise, of *T. rhodesiense* and *T. brucei*, as the wild game are heavily infected with the latter trypanosome.

EPIDEMIOLOGY

Geographical distribution.—The disease is confined to tropical Africa, between 15°N. and 20°S.

Gambiense infection extends from St. Louis in Senegal, north of the Gambia river throughout all the countries on the west coast of Africa down as far as Angola, but there are few endemic areas below 10°S . It extends as far east as Lake Tanganyika in the south, and further north into Uganda, and to the borders of the Anglo-Egyptian Sudan.

Rhodesiense infection has a much more limited distribution; its realm is mainly in the south-east corner of tropical Africa, north, and in few areas south, of the Zambesi river, in Mozambique, Nyasaland, Rhodesia, and Tanganyika.

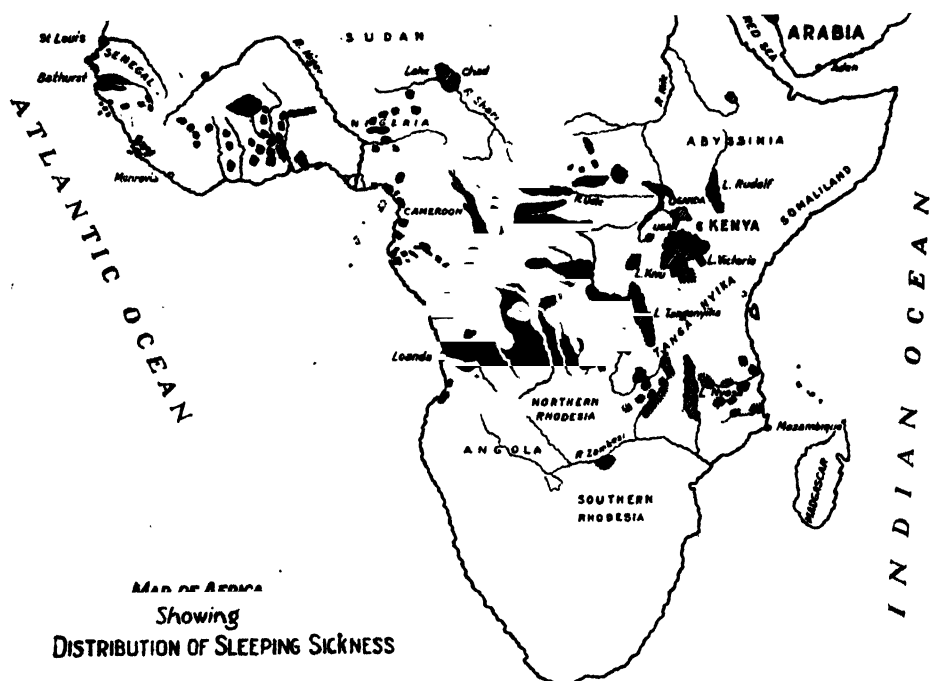


Figure 49

Epidemic features.—The disease is in normal times endemic in the infected areas, but may become epidemic under special circumstances. These circumstances have mainly been associated with the opening up of the country and the migration of African natives into infected areas, but in other cases the infection has undoubtedly been conveyed into new areas by the personnel of exploratory, commercial, scientific, and religious expeditions. Epidemics have nearly always been associated with *gambiense* infection; in *gambiense* areas the incidence of the disease is usually much higher, even during the inter-epidemic periods, than in the *rhodesiense* areas where it is nearly always sporadic. Anything that lowers the general resistance of the population may lead to an exacerbation of the disease in an endemic area.

degree of the infection varies considerably from area to area and within an area from year to year. In some districts in Nigeria, surveys a few years ago (1935) showed a 20 per cent infection rate; in some of these same areas there has been a steady decline, and recent surveys have shown 5 per cent (1938) and 4 per cent (1939) infection rates (Briercliffe, 1940).

The relationship of the disease to wild game has been discussed above.

Local distribution.—In neither form of the disease is the whole country-side infected, but the distribution is always patchy and very local. *Gambiense* infection is confined to riverine areas and the shores of the big lakes, whilst *rhodesiense*, though found in these sites, is also found in drier tracts of country, well away from natural water supplies. In *gambiense* areas, the local inhabitants have from time to time appreciated this fact and moved their villages away from rivers and lakes, but their need for water for themselves and their animals has necessitated their visiting watering clearances where they are liable to get infected.

Effect of temperature.—The geographical distribution indicates that a moderately high temperature is essential, and this observation has been supported by laboratory work. Kinghorn and Yorke (1912) showed that a temperature between 75° and 85°F. was necessary for transmission.

Age, sex, race, and occupation.—There are little differences in the age and sex susceptibility, though men, coming in contact with the infecting tsetse fly much more frequently, are more liable to become infected; however, children who look after grazing herds of goats, sheep, etc., during the hottest part of the day naturally rest in the shade and are very liable to be bitten by tsetse flies. There is also little evidence of any racial immunity, though the inhabitants of the endemic areas suffer a more chronic form of the disease. Occupation is a very important factor; boatmen, fishermen, and others whose work takes them into closer contact with the tsetse are naturally more frequently infected.

PATHOLOGY

Morbid anatomy.—When the parasite is injected, it causes a local inflammatory reaction which subsides in a week or two; the trypanosomes find their way into the blood stream and a septicæmia follows. The trypanosomes and their toxins reach, and probably have some detrimental effect on, every organ and tissue in the body, but the most noticeable effects are on the lymph glands, the meninges, and the central nervous system. The effect is slower in the latter tissues, so that symptoms develop later.

In the lymph glands there is a generalized hyperplasia, with a cellular increase in the lymph follicles, proliferation of the endothelial cells in the sinuses, and leucocytic infiltration, largely of plasma cells, around the blood vessels. This general hyperplasia leads to an increase in the size of the gland, which leads to hypertrophy of the supporting trabeculæ. Later, there is a further increase of fibrous tissue which eventually replaces the lymphoid and the endothelial tissue, and the whole gland becomes sclerosed.

The walls of the blood vessels of the central nervous system, the choroid plexus and vessels of the pia-arachnoid, are damaged by the trypanosomes or their toxins; the trypanosomes penetrate these damaged tissues, and find their way into the arachnoid space and eventually into the brain substance. They produce a generalized lepto-meningitis; there is infiltration of the pia-arachnoid with plasma cells and lymphocytes, and proliferation of the endothelial cells of the capillaries and of the neuroglia cells in the adjacent brain nerve tissue. There is perivascular infiltration by endothelial and neuroglia cells, lymphocytes, plasma and 'morular' cells, and these cells fill the space between the blood vessels and the perivascular sheath that arises from the pia-mater as these blood vessels penetrate this membrane (this space is an extension of the arachnoid space).

The 'morular' cell is a mulberry-shaped cell specifically associated with this disease; its origin is uncertain, but, as it is usually found in, or in close association with, nervous tissue, it has been suggested that it is a degenerated neuroglia cell, and, as it is also occasionally found elsewhere, it is thought that it may also originate from a plasma cell.

There are few changes in the nerve cells, except in the vicinity of the blood vessels; thus the pathological changes in the central nervous system are essentially interstitial and only secondarily parenchymatous.

The gross changes in the lymph glands are redness and swelling in the early stages and later sclerosis, so that they become hard fibrous masses; those most affected are the cervical—particularly in the posterior triangle, the submaxillary, axillary, inguinal, femoral, thoracic, and mesenteric.

On opening the skull, the dura-mater may be found adherent, and there will be a generalized lepto-meningitis mainly confined to the vault and the inner surfaces of the hemispheres; there is an excess of cerebro-spinal fluid; the brain is usually cedematous and the convolutions are flattened; the ventricles may be dilated; and on section a few areas of softening may be found into which hæmorrhages have taken place.

In other organs and tissues, there are few characteristic changes. The spleen is usually slightly enlarged, the liver soft and hyperæmic; there is sometimes a subacute nephrosis; myocardial changes have been described and are well developed in experimental trypanosomiasis in monkeys; and the bone marrow is hyperplastic.

Cerebrospinal fluid.—This will be under normal or slightly raised pressure, 8 to 10 inches of water, and up 30 inches in exceptional cases. It is usually clear, and, although when there is a high cell count it may be cloudy, definite turbidity suggests some bacterial infection.

The most constant changes are an increase in the number of cells, an increase in the protein content, and a decrease in chlorides and sugar. There are normally four cells or less per c.mm.; there may be a slight increase at first, most of the cells being lymphocytes, but the number steadily rises and other cells appear, large mononuclears, plasma cells, morular cells and possibly eosinophils. The count may mount to 2,000 per c.mm. or more; the cell count is apt to be very variable and is not as good a prognostic indicator as is the protein content.

Trypanosomes may be present but are not easily found; it will usually be necessary to centrifuge the fluid and examine the deposit. They are found in larger numbers in *rhodesiense* infections.

A more important change is in the protein content of the fluid. This, normally 0.015 to 0.03 per cent, is always raised, and may be 0.1 per cent (1 gramme per litre), or even higher. It is a constant change not subject to periodic variation and is said to indicate involvement of the parenchyma, whereas a high cell count only suggests inflammation of the meninges.

The changes in the cerebrospinal fluid appear very early in some cases, as early as three months from the first onset of clinical symptoms; they usually precede the development of symptoms referable to the central nervous system, and they are present in every case in which these symptoms are well developed.

Blood.—Trypanosomes may be present in the peripheral blood. They are much more readily found in the *rhodesiense* infection, when they may be present in every field (*see* Diagnosis).

Anæmia is common in the later stages of the disease, and the red cells have a tendency to clump when blood is taken for a red cell count, which fact may make this a very difficult procedure. In the differential leucocyte count, there is relative increase of large mononuclears.

In the urine, albumin is often found early in the disease and it persists throughout; otherwise no specific changes have been reported.

SYMPTOMATOLOGY

It is convenient to divide the symptoms of sleeping sickness into two stages, the early febrile stage and the later stage of cerebrospinal involvement. The division is a convenient one that has survived from the time before the discovery of the causal organism when the two syndromes were not definitely associated, but it should not be forgotten that the pathological process that produces both these sets of symptoms is a continuous one; there are in the first stage many signs and symptoms that suggest meningeal involvement, and it is now well recognized that the characteristic changes found in the cerebrospinal fluid precede the development of the typical second-stage symptoms, by some weeks at least.

Febrile stage.—It must also be remembered that there are cases of entirely symptom-free infection with *T. gambiense*. In a survey, these symptom-free infections may constitute the bulk of the infections identified, and, whilst a certain number of patients will develop cerebrospinal symptoms at a later date, others undoubtedly remain symptom-free for years, if not for ever. This carrier state is more common amongst African natives, but Europeans have been found infected during routine blood examination some years after leaving Africa.

Between these symptom-free and the typical cases, there are cases with all degrees of symptom development.

The typical case is described below :—

The incubation period is not well defined; it may apparently be as short as seven days, though it is usually from two to three weeks before general symptoms appear.

The earliest symptom is the local reaction at the site of the bite of the infecting glossina. Normally, the bite of the tsetse causes local pain followed, in those not used to the bite, by irritation that subsides in a day or two, but in the local inhabitant it will often be unnoticed. The infected bite will cause a sharp local reaction that will usually be first noticed within seven days. A furuncle appears surrounded by an area of redness and induration; this develops into a typical trypanosomal chancre, a dark-red raised button-like lesion about an inch in circumference surrounded by an area of erythema and oedema; it is very painful on pressure; and it lasts two to three weeks. This primary lesion has recently attracted much attention as it is realized that it is the rule in European patients, though less frequently reported by African natives, that it provides an opportunity for early diagnosis as the trypanosomes are easily demonstrated in it, and that it thus helps the institution of early treatment.

Fever may accompany this primary lesion or follow very shortly after its first appearance. There is sudden high fever which reaches 103°F. or so within the first 48 hours; high fever continues for about a week and then the temperature falls and remains normal or low for a few days before rising again for a few more days. After this the temperature

chart shows an irregular low pyrexia for some months, with perhaps evening rises to 99° or 99.5°F. and occasional short bouts of high fever; then the fever gradually disappears.

The rash is inconstant and irregular. It would not easily be seen on the dark skin, so it is mainly in Europeans that it has been reported. It may appear at any time during the disease, but is most common soon after the onset of the fever. It is usually a circinate erythema that appears in patches on the trunk, face, or limbs; it may be transient or persistent, and when it disappears it leaves no traces, and there is no desquamation.

The enlargement of the lymphatic glands is one of the most characteristic signs of the first stage; in the African native sufferer, it may be the only sign by which the disease can be recognized. The glands most easily seen are those in the posterior triangle of the neck; the other cervical glands, the glands in the groin, popliteal space, and axilla, and the epitrochlear glands are others easily examined and they will frequently be found enlarged.

The gland is at first soft, mobile, and rubbery, discrete, and painless. Enlargement of the glands in the posterior triangle of the neck may be due to pediculosis or other scalp infections common in African natives, but in this case they will be more painful, less movable, and possibly matted. Later, the enlargement subsides and the glands become hard sclerosed masses.

Other signs and symptoms include localized and transient œdema of different parts of the body, most commonly of the face, including the eyelids, neck, ankles, and in the vicinity of the initial lesion. The spleen and liver are both enlarged in many cases, but concomitant malaria can seldom be entirely excluded.

Tachycardia is a constant sign and the pulse rate seldom falls below 100, even in the afebrile periods. The blood pressure is also low, and there are other signs of myocardial involvement, such as palpitation and shortness of breath on slight exertion.

Deep reflexes may be normal but are often exaggerated; hyperæsthesia is very common, and a particular form of this is known as Kérandel's sign; this is a delayed-action hyperæsthesia, in which, following pressure or a slight knock, severe pain comes on after a few minutes. There may be paralysis of single muscles or groups of muscles; facial paralysis is not uncommon. Neuralgias often occur.

Asthenia develops early and is often very pronounced. Severe headache is almost constant. The patient is drowsy during the day and restless at night. Depression amounting to melancholia, irritability, emotional imbalance, deterioration of memory and of general intellectual powers are not uncommon.

During this stage the patient may become extremely debilitated and emaciated, and die of some intercurrent infection.

There are a few cases reported in which the disease was undoubtedly arrested at this stage, without specific treatment, but generally after lasting a variable time, usually six months to a year (but sometimes longer, even up to 7 years) in *gambiense* infection and four months or less in *rhodesiense*, it passes into the next stage.

Meningo-encephalitic stage.—The onset of this stage will be indicated by an increasing lassitude and general indifference to surroundings, with

PLATE IX (Sleeping sickness)



Fig. 1—Early stage.



Fig. 2.—Glandular enlargement.

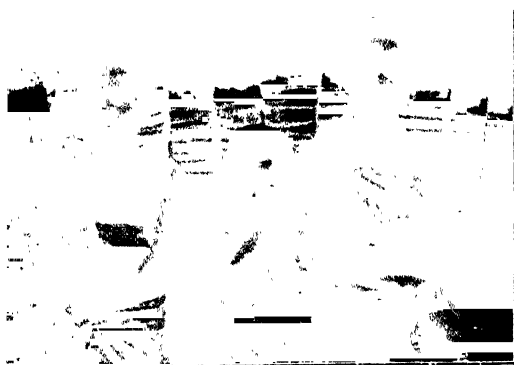
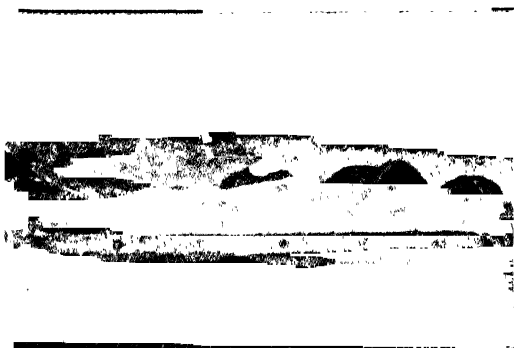


Fig. 3.—More advanced first stage.

Chagas's disease.



a subsidence rather than an exacerbation of the more acute symptoms of the early stages; the tachycardia becomes less pronounced but other cardiac manifestations develop, and there is usually considerable hypertrophy and dilatation. The gait is slow and shuffling, the speech slow and slurred, there are fine tremors of the hands, of the tongue, and occasionally of other muscular groups. Intolerable pruritus is common. The latent period of response to questioning is prolonged, and insistence has to be exerted, but the intelligence is not seriously impaired at first. The patient is somnolent but can be aroused; his indifference to food—which he will take if it is given to him, though he may fall asleep in the process of mastication—leads to malnutrition with its sequelæ. Later, convulsions which may lead to temporary paralyses of groups of muscles, and psychical disturbances, mania and delusions, may occur.

The characteristic appearance, the morose expression, the half-closed puffy eyelids, the drooping corners of the mouth from which saliva dribbles, and the extreme emaciation, is a picture familiar to all readers of textbooks of tropical medicine, but in the majority of cases even this stage of the disease will be much more subtle in its manifestations.

There is little change in the reflexes until almost the terminal stage, when the knee jerks, after a period of over-brisk response, may be absent, and the sphincter controls lost. The pupils usually react normally.

Optic atrophy has been described, even in the absence of any arsenical treatment, and there may be œdema of the disc due to meningeal involvement, with or without increased intracerebral pressure.

This stage seldom lasts more than a year if no treatment is given, though there have been instances of temporary remission with consequently a much longer duration. In more severe cases the end will come within three or four months. Death in convulsions has been reported, but the usual termination is from emaciation and complications, *e.g.* bed-sores, bladder infection, pneumonia, etc.

DIAGNOSIS

The common clinical signs and symptoms of the early stages are the trypanosome 'chancre', irregular fever, glandular enlargement—particularly in the neck, the rash, and Kérandel's sign, but it will always be advisable to confirm the diagnosis by finding the trypanosome.

Certain presumptive laboratory tests will be of value only in cases in which the clinical signs are not characteristic, because in a typical case they add little weight to the provisional diagnosis, and parasitological confirmation will still be necessary.

To carry out a survey in an endemic area, after a preliminary selection of suspected cases by gland palpation, gland puncture and thick-film examination will be the only practical methods.

In the later stages, the parasites in the blood are very scanty and the glands may be sclerosed. In these cases the cerebrospinal fluid will be the only medium of diagnosis; even in the absence of trypanosomes, which are always difficult to find, characteristic changes in this fluid are considered to be diagnostic.

The confirmatory and presumptive methods of diagnosis can be summarised as follows :—

Confirmatory methods.—(i) Direct examination of fluid from the primary lesion (trypanosome chancre).

(ii) Gland puncture.

(iii) Examination of the peripheral blood, (a) direct coverslip examination, (b) by the thick-film method, and (c) after triple centrifugalization.

(iv) Lumbar puncture.

(v) Animal inoculation.

Technique.—(i) The indurated margin of the lesion is pricked with a needle and the fluid that exudes is examined under a coverslip, or a smear is made, stained by Giemsa's method, and examined.

(ii) The skin over the gland to be punctured is sterilized, and the gland is held firmly with the left hand while a hypodermic needle of wide bore is thrust into the gland; the needle is passed backwards and forwards in several directions through the gland substance, which is thus forced up the bore of the needle. The needle is withdrawn, and its contents blown on to a slide by attaching the syringe to it and examined fresh and after staining.

(iii) (a) A drop of blood taken from the finger or ear-lobe is mixed with an equal quantity of citrate saline and examined under a vaseline-ringed coverslip with a 1/6 inch objective; the attention will be drawn to the trypanosome by the movement of the red cells.

(b) The thick-film methods of examining for malaria parasites (*see* p. 87) can be utilized; the author has no information regarding the suitability of Field's rapid-staining method for this purpose.

(c) About 5 c.cm. of blood is withdrawn, placed in a centrifuge tube containing 1 c.cm. of 2 per cent sodium citrate solution, and centrifuged at low speed (1,000 revolutions per minute) for ten minutes; this will throw down the majority of the red cells. The supernatant fluid is removed and centrifuged again at the same speed until the rest of the red cells and most of the leucocytes are deposited. The supernatant fluid is again removed and centrifuged a third time at a rapid speed—2,000 revolutions per minute. The deposit is now examined, directly under a coverslip and after staining.

(iv) The cerebrospinal fluid can be obtained by either lumbar or cisternal puncture. After rapid centrifugalization, the deposit is examined for trypanosomes. Trypanosomes are seldom found in *gambiense* infection, but a definite diagnosis can be made on the cellular findings and the biochemical changes. A lymphocyte count of 50 per c.mm. or more, and a protein content of 0.03 per cent are claimed by some workers to be diagnostic; the presence of morular cells will considerably strengthen the evidence.

Pandy's test is a simple and most useful test to carry out in the field. One drop of cerebrospinal fluid is dropped into 2 c.cm. of carbolic acid solution (1 part pure phenol in 15 parts of distilled water); the appearance of a bluish-white cloud constitutes a positive result, which indicates an excess of globulin. In a case in which trypanosomes have been found in the glands, this test will show whether the central nervous system is involved; it is very sensitive and is usually positive long before the development of physical signs of involvement of the central nervous system.

(v) Of laboratory animals, mice, rats, guinea-pigs and rabbits are all susceptible to infection, and strains can be maintained for long periods by passage through these animals, but to establish a strain in the laboratory, it is usually necessary to make the first passage through a monkey, *Silenus rhesus* or some species of *Cercopithecus*. The deposit of 5 c.cm. of citrated triple-centrifuged blood should be inoculated intraperitoneally into a monkey; subsequent passages are made from the monkey's blood, 0.5 to 3 c.cm., according to the size of the animal to be infected. Cerebrospinal-fluid deposit can be used in the same way.

A differential diagnosis between *T. gambiense* and *T. rhodesiense* can be satisfactorily made only by animal inoculation; in the latter, the

infection is much more virulent, and posterior-nuclear forms will appear (*vide supra*).

The presumptive tests.—(i) The clumping of the red cells, when blood is taken in normal saline for doing a blood count, occurs very constantly in this disease and seldom in other diseases. The clumping may be noticed in the gland-puncture slide when this is examined fresh, and should at once arouse suspicion, so that the gland juice can be examined for a longer period than usual before being pronounced negative.

(ii) Brown's adhesion phenomenon depends on the fact that, in the presence of immune serum, platelets and other small particles (*e.g.* bacilli) will adhere to trypanosomes; it is claimed that the test is species-specific.

(iii) The serum-formalin test is carried out in the same way as for kala-azar (*see* p. 164 and plate VI).

The 'positive' result is not as clear-cut as in kala-azar, though a definite change occurs in all advanced cases of sleeping sickness, and many other conditions produce confusing results, so that it is not a test of great value in the human disease, as it is in animal trypanosomiasis, *e.g.* camel trypanosomiasis in which it is the routine diagnostic procedure.

TREATMENT

Historical.—From the earliest days, arsenic in one form or another has been considered a specific for sleeping sickness. *Liquor arsenicalis* was at one time used in increasing doses up to the point of intolerance; later, sodium arsenate was given by injection, but the beneficial effect was found to be transient. The synthetic arsenical, atoxyl (sodium *para*-aminophenyl arsonate), a proprietary preparation, used in certain skin diseases, was found by Thomas, working at the Liverpool School of Tropical Medicine, to have a sterilising effect on experimental trypanosomiasis in mice. The early success of these investigations did much to encourage the German chemists to persevere in their search for the *therapia magna*, the first stage of which ended in the discovery of salvarsan by Ehrlich in 1910.

In 1908 Plimmer and Thomson showed that intravenous sodium antimonyl tartrate caused trypanosomes to disappear from the blood of experimental animals; Kérandel claimed to have cured himself with potassium antimonyl tartrate after atoxyl had failed.

Many other arsenical antimonyl preparations were introduced and tried, but none had the success of atoxyl, which however had its strict limitations (*vide infra*), until 1922 when the complex organic urea preparation, Bayer 205, or Germanin, was introduced; this still has an established place in the treatment of the disease. A few years later tryparsamide, sodium *N*-phenyl-glycinamide-*p*-arsonate, was prepared by Jacobs and Heidelberger and has proved one of the most powerful of the arsenical preparations yet used in the treatment of sleeping sickness. Orsanine (Fourneau 270), 4-acetyl-amino-2-hydroxy-phenyl arsonic acid, was introduced by Ledentu and Daude in 1926. The most recent additions to the trypanocidal drugs are the aromatic diamidines; of these 4:4'-diamidino diphenyl ethylene has had the most extensive trial, but there are indications that it does not reach the cerebrospinal fluid. In this respect, 4:4'-diamidino diphenoxy pentane and propane are believed, from more limited experience, to be superior. It was again at the Liverpool School of Tropical Medicine, by Yorke (1940) and his co-workers, that this group of drugs was introduced.

An 'incident' in the history of the treatment of sleeping sickness was the wide publicity given in the early inter-war period to the now finally discarded salvarsanised serum treatment.

Since the best of the drugs so far used will only cure about 50 per cent of the patients treated in the late stages of the disease, and since many drug-resistant cases are encountered at all stages, the history of the treatment of this disease is obviously still in the making.

Specific drugs and dosages.—At the present day, the only specific drugs that have survived an extensive trial are—atoxyl, which is now

practically obsolete, orsanine, and germanin (or antrypol, a British product which is identical with germanin*), for treatment in the first stage, and tryparsamide for the meningo-encephalitic stage; orsanine is also used in the latter stage but its value is very limited. The antimonials may be looked upon as an adjuvant treatment in arsenic-resistant cases. The aromatic diamidines show considerable promise, but have not yet undergone the test of time.

Atoxyl is given in a 10 per cent solution in sterile distilled water, in doses of 10 to 15 mg. per kilogramme body-weight, weekly for six to ten weeks. With larger doses, higher cure rates can be expected, but toxic sequelæ are correspondingly more common.

Orsanine is given subcutaneously, intramuscularly, or intravenously in a 20 per cent solution in sterile distilled water, in doses of 20 to 35 mg. per kilogramme body-weight; the maximum individual dose is usually considered to be 2 grammes. The injections are given weekly for ten to twelve weeks. It is less toxic and more efficient than atoxyl in sterilizing the peripheral blood in the early stages, but it is far less efficient than tryparsamide in the meningo-encephalitic stage, though it is still used in this stage.

Tryparsamide is given intravenously in a 20 to 40 per cent solution in sterile distilled water, in doses of 20 to 40 mg. per kilogramme body-weight, up to a maximum individual dose of 3 grammes in an adult, at weekly intervals for 10 weeks. Chesterman recommends larger doses, of the order of 60 mg. per kilogramme in adults, with a maximum of 4 grammes for an individual dose. This drug has a relatively poor trypanocidal action and is therefore not given in the early stages, but it appears to possess special powers of penetrating nervous tissues, and is therefore the drug of choice in the late stages of the disease.

Antrypol, or germanin, is given intravenously in a 10 per cent solution in sterile normal saline, in doses of a gramme for an adult, twice or thrice weekly, up to a total dose of 10 grammes.

4 : 4'-diamidino diphenyl ethylene, diphenoxy pentane, and diphenoxy propane, the members of the diamidine group that have so far been used, are given in a 2 per cent solution in sterile distilled water, in doses of 1 mg. per kilogramme body-weight thrice weekly, up to 15 injections.

Antimony preparations.—Sodium antimonyl tartrate has been largely superseded by other less toxic drugs. The trivalent foudin and the pentavalent neostibosan have been used with some success, and are given in the dosages used in leishmaniasis (*see* p. 168).

Toxic effects.—All the pentavalent arsenical drugs may give rise to toxic symptoms even when given in moderate doses, but the likelihood of this occurring increases with the dose. Each drug has its own specific range of toxicity, and individual susceptibility is a variable factor.

Occasionally, severe diarrhoea and vomiting will occur; liver disturbances and dermatitis are rarer than with the trivalent arsenicals, but do occur. Visual disturbances are usually the limiting factor; these may be serious. The earliest symptoms are dimness of vision, contraction of the visual field, and sometimes flickerings. Later, blind spots will appear and eventually there will be complete blindness.

* A French product moranyl (Fournau 309) is also identical with germanin.

Little change will be seen by use of the ophthalmoscope until permanent and irreparable damage is done. Therefore a patient having tryparsamide should have his vision tested before the course is started, and then before *each* subsequent dose; if there is any deterioration of vision, the tryparsamide should be stopped immediately.

If arsenic treatment is suspended immediately the early symptoms appear, the vision will usually improve again.

Optic atrophy is more likely to occur in advanced second-stage cases than in early cases, and is due both to the disease—which alone will occasionally produce it—and to the treatment.

Sodium thiosulphate (10 c.cm. of a 20 per cent solution, given intravenously on alternate days) has been used, with considerable success in some cases, in the treatment of this form of arsenical poisoning.

The most important toxic effect of antrypol is due to idiosyncrasy that occurs in a very small proportion of patients; it is easily avoided by giving 1 c.cm. of the solution first and then waiting a few moments before giving the remainder. Idiosyncrasy is indicated by an almost instantaneous collapse. Antrypol also damages the renal epithelium and often causes albuminuria after a few doses have been administered; this is usually transitory and disappears when the injections are discontinued, but may recur when they are started again. More serious damage may be done, and epithelial casts and blood may appear in the urine. If the condition is ignored, it may progress, causing anuria and death. Necrotic changes in the suprarenal cortex, and, as a rare effect of this drug, dermatitis have been reported.

Certain alarming, both early and late, toxic effects from 4 : 4'-diamidino diphenyl ethylene have recently been reported.

The treatment of the case.—Early institution of treatment is very important as the trypanosome is very much more easily killed before it has established itself in the meninges and brain. The *gambiense* infection is much more amenable to treatment than the *rhodesiense*, which is very apt to become arsenic-fast.

In the first stage of either infection, antrypol is the drug of choice, but in *gambiense* infection orsanine may be used as an alternative. Yorke considers that the danger of making a *rhodesiense* case arsenic-resistant should deter one from using any arsenic drug in the early stages.

Pandy's test (*v. s.*, p. 210) is of great value in determining whether a patient with trypanosomes in his blood, or gland juice, can be treated as an out-patient with antrypol or whether he must be admitted to hospital for treatment with the more toxic tryparsamide.

In the meningo-encephalitic stage, tryparsamide is the only really satisfactory drug. Orsanine will undoubtedly produce cures in this stage, and claims as high as 50 per cent have been made for it, but it is generally agreed that it is inferior to tryparsamide.

In arsenic-resistant cases, the physician must resort to antimony preparations, at least as alternating courses, and to antrypol, though the latter has a relatively poor action when once changes have occurred in the cerebrospinal fluid.

The art of the treatment of this disease resolves itself into striking a balance between the toxic and the efficient dose of the trypanocidal drugs, and playing them in such a way that the infection does not become drug-resistant—this drug-resistance is not confined to the arsenic compounds. Inadequate dosage certainly tends to produce drug-resistance. Chesterman

takes the view that in the treatment of an otherwise fatal disease one should be prepared to risk the complications that larger doses may cause. Obviously this is a matter of circumstances as well as opinion.

General and subsidiary treatment.—The circumstances are not usually such that the patient can be confined to bed, but when this is possible it should certainly be done, at least during the febrile stage. In both this and the later stages, good nursing is of the greatest importance; in the latter in particular, bed-sores, hypostatic pneumonia, etc., are very likely to occur unless great care is taken.

Concomitant infection, such as hookworm, malaria, etc., must first be treated to allow the specific drugs to exert their full action.

Drug-resistance.—This is an interesting phenomenon, the full explanation of which has not yet been given. Drug-resistance may be a function of the parasite, or of the host. It is easier to conceive of it as a function of the latter, but it is believed in this case to be one of the former.

After treatment by the pentavalent arsenic compounds, it is sometimes found that the infection from which the patient is suffering is arsenic-resistant, that is to say, further treatment by any of the pentavalent arsenic compounds, and to a less extent the pentavalent antimony compounds, will not affect the trypanosomes. If this strain of trypanosome is transmitted to another man, or to an animal, it still retains its arsenic-resistant character; in fact, no multiplication of animal passages or alternation of the insect vectors will alter the arsenic-resistant character of the strain.

Antrypol-resistant strains have also been isolated, but not so readily.

Drug-resistant strains are more frequently encountered in *T. rhodesiense* than in *T. gambiense* infections, but they have been found in the latter, in areas where wholesale inadequate treatment has been undertaken. This suggests to the writer that arsenic-resistance in a trypanosome is born and not made, for in *rhodesiense* infection the cycle is probably not man—tsetse—man, but animal—tsetse—animal with infection of man as a sporadic incident; from this *cul-de-sac* the trypanosome stains do not as a rule return into circulation.

The theory that appeals to the writer is as follows: In man (and in animals) there are innumerable strains of trypanosome with slightly varying characteristics, living in biological competition; when a number of strains are infecting a single individual, one strain predominates but the others are still there ready to come to the fore when their stronger rivals are knocked out (cf. malaria). Eventually, all drug-susceptible strains are knocked out; drug-resistant strains are thus *selected*, and not *made*. If this theory is established, some revision of the principles of treatment will be necessary.

PREVENTION

Before considering preventive measures it will be as well to review the essential factors in transmission; these are (i) the trypanosome and its 'reservoirs', (ii) the tsetse fly, (iii) susceptible man, and (iv) contact between the tsetse and man.

Preventive measures must be considered in connection with each of the factors:—

(i) **The trypanosome and its 'reservoirs'.**—In *gambiense* infection man is the main reservoir of infection and attempts have been made to reduce this reservoir by widespread blood-sterilizing campaigns, in which very large numbers of people are given single, or at any rate only a few,

injections of some arsenical compound, *e.g.* orsanine. Cure is not effected, but temporary sterilization, or at any rate a marked reduction in the number of trypanosomes in the blood, will be achieved. The objection to this procedure is the danger of the development of arsenic-resistant strains; it is still practised in some colonies but is not to be recommended. On the other hand, treatment campaigns that aim at giving a full course and curing the patients will help to reduce the reservoir of infection. The possible wild-game reservoir of *rhodesiense* infection opens up controversial subjects which it would be out of place to raise here.

(ii) *The tsetse fly.*—*G. palpalis* remains near the shores of lakes and the banks of rivers. Burning or otherwise destroying the bush and undergrowth that provides shade for tsetse larvæ at river crossings and watering places, may render the ground unsuitable for breeding, but is very expensive, wastes timber, and may encourage soil erosion. Numbers can be greatly reduced by the regular catching of flies with hand-nets in selected blocks of bush (Symes and Southby, 1938). Trapping and other special methods have been introduced in special circumstances.

(iii) *Susceptible man.*—Individual protection can be achieved by the administration of antrypol, or germanin; two grammes will give protection for at least three months. In the Belgian Congo a large-scale experiment, in which 1 gramme per adult was given every three months, had some apparent success.

Rules have from time to time been put into operation to prevent migration of susceptible natives into infected areas, but are difficult to enforce.

(iv) *Contact between the tsetse and man.*—As the tsetse bites during the day, it is difficult to devise means of protection. Clothing certainly helps to protect the European sojourner. Night travel has in the past been resorted to in order to avoid infection.

The location of settlements away from rivers and lakes, and the aggregation of the population into relatively large villages, as opposed to wide distribution in scattered homesteads, are measures that are now being adopted. It is possible to make wide clearings around these villages, and of course this should be extended to the roads as far as possible.

Gibbins (1941) has recently investigated the use of rod-shaped clearings along streams, watering places and road crossings. These clearings discourage *G. palpalis* from lingering to bite man.

As in the case of almost every tropical disease, the economic, agricultural and nutritional aspects of control loom large, and the subject has to be studied from all these points of view.

PROGNOSIS

Untreated *gambiense* infection may run a very chronic course of some years' duration, whereas *rhodesiense* infection usually runs a rapid course of a few months' duration; but there are exceptions in each instance.

Prognosis in the treated case will depend on the stage at which the diagnosis is made and treatment instituted, on the species of infecting trypanosome, and on the treatment given. In the early stages the prognosis is much better than in the late stage when the meninges are involved, in either infection, and in *gambiense* infection even in the second stage, at least 50 per cent will respond to tryparsamide, but in *rhodesiense* infection the prognosis is usually much graver.

To this general rule there are exceptions; some strains of *T. gambiense* are very resistant to treatment, and there are strains of *T. rhodesiense* that respond readily.

REFERENCES

- BRUCE, D. (1895) *Preliminary Report on the Tsetse-Fly Disease or Nagana in Zululand*. Bennet and Davis, Durban.
- Idem* (1910) Discussion on Human Trypanosomiasis. *Brit. Med. J.*, ii, 864.
- CONSON, J. F. (1939) A summary of the work of the Research Scheme on *Trypanosoma rhodesiense* during the years 1930 to 1938. *East African Med. J.*, 16, 84.
- EVANS, G. (1881) On a Horse Disease in India known as 'Surra' probably due to a Hæmatozoon. *Vet. J.*, p. 1, *et seq.*
- FORDE, R. M. (1902) Some clinical notes on a European patient in whose blood a Trypanosome was observed. *J. Trop. Med. and Hyg.*, 5, 261.
- GIBBINS, E. G. (1941) Studies on the bionomics, control and natural infectivity of the riverine *Glossina palpalis* sub-species *fuscipes* Newstead in the West Nile district of Uganda. *Ann. Trop. Med. Parasit.*, 35, 195.
- KINGHORN, A., and YORKE, W. (1912). On the influence of meteorological conditions on the development of *Trypanosoma rhodesiense* in *Glossina morsitans*. *Ann. Trop. Med. and Parasit.*, 6, 405.
- KLEINE, F. K. (1909) Positive Infektionsversuche mit *Trypanosoma brucei* durch *Glossina palpalis*. *Deut. med. Woch.*, 35, 469.
- LEDENTU, G., and DAUDE, J. (1926) .. Treatment of Trypanosomiasis by Fournieu 270. *Ann. Inst. Pasteur*, 40, 830. (Abstract—*Trop. Dis. Bull.*, 1927, 24, 565.)
- LIVINGSTONE, D. (1857) *Missionary Travels and Researches in South Africa (Tsetse-Fly)*, pp. 80, 571. John Murray, London.
- PLIMMER, H. G., and THOMSON, J. D. (1908). Further results of experimental treatment of Trypanosomiasis in rats. *Proc. Roy. Soc. Ser. B.*, 30, 1.
- STEPHENS, J. W. W., and FANTHAM, H. B. (1910). On the peculiar morphology of a Trypanosome from a case of sleeping sickness and the possibility of its being a new species (*T. rhodesiense*). *Ann. Trop. Med. and Parasit.*, 4, 343.
- SYMES, C. B., and SOUTHEY, R. (1938). The Reduction of *G. palpalis* in a Lake Shore Area by the 'Block' Method. Nairobi. (Abstract—*Trop. Dis. Bull.*, 1939, 36, 740.)
- YORKE, W. (1939) Trypanosomiasis. *British Encyclopædia of Medical Practice*, 12, 263. Butterworth and Co., Ltd., London.
- Idem* (1940) Recent work on the chemotherapy of protozoal infections. *Trans. Roy. Soc. Trop. Med. Hyg.*, 33, 463.

CHAGAS'S DISEASE, OR SOUTH AMERICAN TRYPANOSOMIASIS

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Definition.—South American trypanosomiasis, or Chagas's disease, is a disease that is usually acute in its early stages characterized by local swellings, fever, adenitis and anæmia, and later develops varied chronic manifestations, cardiac, nervous or myxœdematous; it mainly affects children, and it occurs in South and Central America. It is caused by *Trypanosoma cruzi* which is transmitted to man by reduviid bugs of the family Triatomidæ, notably *Triatoma megista* and *Triatoma infestans*.

Historical.—The history of this disease is almost unique in that the causal organism and the mode of transmission were discovered in the laboratory before the disease was recognised clinically. Carlos Chagas and Cruz demonstrated the trypanosomes in reduviid bugs and transmitted the infection to monkeys; later, Chagas discovered the disease in children in Brazil. Recently, the disease has been shown to be more widespread than was at first supposed, and to occur in a number of other South and Central American countries. Further, Triatomidæ have been found infected in many American countries, e.g. Texas (Packchanian, 1939), where the disease has not yet been found, and many insects other than the Triatomidæ have been shown to be potential vectors, e.g. *Triatoma sanguisuga ambigua* (Packchanian, 1940).

ETIOLOGY

The causal organism.—This is now classed as a trypanosome, but in view of certain differences between it and other trypanosomes, it was at one time placed in a separate genus, *Schizotrypanum*.

Morphology and staining.—It has two forms, a flagellate form in the transmitting insect and in the blood of the vertebrate host, and a leishmania form in the solid tissues of the latter. The flagellate form passes through various developmental stages, appearing as a trypanosome, a crithidia, and a leptomonas in the insect vector, and also probably in the vertebrate hosts' tissues.

In the blood, only trypanosome forms are seen; these may be either short stumpy or long slender forms. In their morphology and staining, they differ very little from the trypanosomes of the African disease (*q.v.*), but they are slightly larger, measuring about 20μ as a rule. The stained specimen assumes a characteristic C shape (see plate II).

When they invade the host cells, they lose their undulating membrane and flagellum, and become leishmania forms (see KALA-AZAR), 1.5 to 4μ in diameter. They multiply rapidly by binary fission and destroy the host cell which eventually bursts, when they may find their way into other cells, or back into the lymphatic fluid and blood, but it is only trypanosome forms that are seen in the latter.

Distribution in the human host.—As noted above, the trypanosome forms are found in the blood, though in the human host they are very scanty in the peripheral blood. The leishmania forms are found mainly in the endothelial cells of the capillaries and lymphatics, and in the heart muscle, but they also invade the cells of the skeletal muscles. They thus occur in nearly all the organs and tissues of the body, spleen, liver, suprarenals, ovaries, testes, thyroid, brain, bone marrow, mucous membranes, and subcutaneous tissue. They have also been found in the cells of the epidermis.

Transmission.—There are many potential vectors, but, as far as is known at the present time, two species are mainly responsible for the transmission of the disease to man, namely *Triatoma megista* and *Triatoma infestans*. In the endemic areas these bugs are repeatedly found infected in nature, sometimes to the extent of 90 per cent of specimens examined. They have also been found infected in countries where few or no cases have been discovered, e.g. in Mexico, where recently a very few cases have been reported, and in California, Texas, and Arizona, where no case has yet been found. Further, a trypanosome, apparently identical with *T. cruzi*, has been found in nature in a large number, at least twenty, of species of *Triatomidae* and many of these have been shown experimentally to be potential vectors.

Other arthropods, e.g. *Cimex*, *Ornithodoros*, *Rhipicephalus*, have also been shown to be capable of maintaining the trypanosome in their intestinal canals, and of transmitting it.

The infection is said to be transmitted from the adult bugs to their progeny in the ovum, but it is more likely that the larvæ are infected by the faeces of adults.

Mechanism of transmission.—The bug becomes infective eight to ten days after feeding, at any nymphal stage or in the adult stage, on an infected vertebrate, and retains the infection for the rest of its life, up to

two years. The trypanosome multiplies and passes through different developmental stages to become a metacyclic, short stumpy, form which is passed in the fæces. The salivary glands are not infected, and transmission is not effected by the bite, as was at first supposed, but by the metacyclic trypanosomes that are passed in the fæces of the bug being rubbed into the wound made during the bite, and possibly by contamination of the conjunctivæ with the fingers. The irritation caused by the bite will lead to scratching, so that either of these events is a likely sequel.

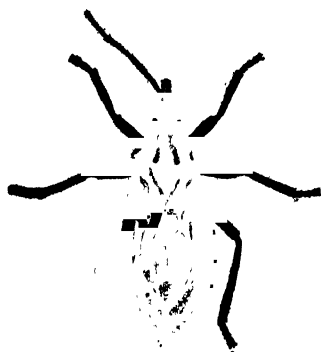


Figure 50: *Triatoma megista*.

Animal reservoirs of infection.—There is a long list of wild animals that have been found infected and/or shown to be capable of sustaining the infection, notably the armadillo and the opossum.

Domestic animals are also found naturally infected, *e.g.* the cat and the dog, in a high percentage. It seems probable that wild animals are the main sources of infection, as triatoma have been found living in their burrows.

Cats and dogs are infected by feeding on infected rodents.

EPIDEMIOLOGY

Geographical distribution.—All the earliest cases were reported from the Minas Geraes district of Brazil, and in fact, as pointed out by Yorke (1937), only a little over a hundred cases had been reported from anywhere else, up to that date, despite the very wide distribution of the infection in animals and of the potential insect vectors. However, during the last few years more cases have been reported from many South American countries, Argentina, Uruguay, Peru, Venezuela, and Chile, from Panama, Guatemala, and San Salvador, in Central America and recently from Mexico.

No human case has yet been reported from the United States.

After Brazil, Argentina has provided the largest number of cases, and this had reached about 500 by 1940 (Mazza). In most other countries only isolated cases have been found, even after systematic investigation.



Figure 51

Epidemic features.—The disease is sporadic and occurs mainly amongst the infants and young children of the lower classes in the endemic areas. Children of either sex are attacked and usually the first symptoms appear before they are two years old. Older children and adults are occasionally affected. The disease is commoner in country districts than in towns.

PATHOLOGY

The type of lesion that is produced by the parasite is fairly constant, but the distribution amongst the organs and tissues of the body is very variable; this accounts for the diversity of the clinical manifestations.

Cells in different parts of the body, mainly endothelial cells of the capillaries and lymphatics, and the reticular cells of other organs and tissues, are invaded by the trypanosomes which develop into leishmania forms, multiply rapidly, and destroy the host cell, converting it into a kind of cyst. This cyst bursts and the parasites are carried by the blood into other organs and tissues.

There appears to be an early brisk tissue reaction during the period of invasion; *e.g.* in the heart in a child who died within a few weeks of the first symptoms, there was an invasion of histiocytes and monocytes in the reticular tissue between the heart muscle fibres, but parasites were so scanty that only one or two were discovered; later, however, the local response to invasion appears to be very slight and large cyst-like bodies containing numerous multiplying leishmania forms are seen, with very slight reaction beyond a little fibrosis occurring in the surrounding tissues.

The organs affected are mainly the heart, the brain, the suprarenals, ovaries and testes, the thyroid, the lymphatic glands, and the liver. The parasite also has a predilection for skeletal muscles.

Most of the chronic changes described have been in the thyroid, but it now seems very doubtful if these are really due to the trypanosome infection (*vide infra*).

In the heart, interstitial fibrosis of the myocardium, with parasites still present in a few cases only, is probably the commonest chronic lesion.

SYMPTOMATOLOGY

As in most other infections by parasites of the family Trypanosomidae, the reaction to the infection is very variable, and it seems certain that many infections do not reach the clinical threshold. In the few experimental infections the symptoms have usually been mild and temporary.

An early acute and later chronic form of the disease are recognized.

In the acute form, which is nearly always in children, after an incubation period of 10 to 20 days, there is a sharp febrile attack of moderate intensity which lasts for about three weeks. At the beginning of this attack, oedema of one side of the face may occur. This oedema may spread to the neck, shoulders, chest, and arms, and in a few cases general anasarca has been reported. This unilateral swelling of the face, which is usually most noticeable in the loose cellular tissue of the eyelids, is known as Romana's sign. The unilateral nature of this sign suggests that it is in some way associated with the original point of entry of the infection, at the site of the bite, or *via* the conjunctiva; it does not appear to be the immediate reaction to the bite, but rather of the nature of a later allergic reaction when the general infection is established. There is often a morbilliform rash on the arms and trunk.

Other accompaniments of the acute attack are dyspnoea, cyanosis, and other acute cardiac and cerebral symptoms. The liver is often enlarged and sometimes the spleen. Lymphatic glands in the neck and other parts of the body are sometimes slightly enlarged. Death may result after a very short illness. It was originally claimed by Chagas that, if the child recovers from the acute attack, it always passes into the chronic stage.

About the chronic form, there is considerable confusion in the literature, since the authenticity of the original picture of this stage, as painted by Chagas, is seriously questioned. Endemic goitre and cretinism are very common in the district of Minas Geraes where Chagas first discovered the disease, and it appears that the picture he painted is really not chronic Chagas's disease, but endemic hypothyroidism. A similar condition has not been observed in any of the other non-goitrous districts where Chagas's disease is endemic. Further, there is no experimental evidence that this trypanosome has any predilection for the thyroid gland, as it undoubtedly has for heart muscle, for example.

If this view is accepted, there is little left of the chronic syndrome. The patients who have been found infected, often accidentally and/or at post mortem, have shown a variety of symptoms, but the most commonly recurring ones are those associated with a chronic form of heart disease, with alterations in conductivity and disturbances in rhythm.

Early death from chronic fibrotic changes in the heart is common in the districts where infected bugs are found, and, in the absence of any other obvious cause for this, and in view of the facts that many of these persons have been shown to be infected and that this trypanosome undoubtedly has a predilection for heart muscle, it is tempting to associate these two observations.

Chagomas.—This term has been introduced recently by Mazza to describe certain swellings that occur in the skin as a result of infection with *T. cruzi*. He describes the pathological changes as a fatty necrosis in the epidermis and subcutaneous tissues. The swellings produced are firm, sometimes of cartilaginous hardness; they move freely over the underlying muscles; and they are often of a reddish-purple colour. They may occur at the original site of the entry of the parasite following a bite, in which case Mazza calls them inoculation chagomas, or they may be metastatic, appearing in large numbers in different parts of the body a month or so after the primary lesion. The inoculation chagoma appears within about a week of the inoculation and persists for some weeks, and leishmania forms of the parasite can be found in it.

DIAGNOSIS

The clinical diagnosis in a typical case does not present any particular difficulties. Romana's sign in children and the more recently described chagomas in both adults and children will arouse strong suspicion. During the first few weeks of the infection, confirmation is not usually difficult; in a large percentage of cases, trypanosomes can be found in the blood, by direct examination or by the triple centrifugalization method (see p. 210). The leishmania forms can also be demonstrated in the chagomas.

Later, animal inoculation or xeno-diagnosis will be necessary.

For the former, young animals, guinea-pigs or better still puppies, are inoculated with the deposit after triple centrifugalization of 10 c.cm. of blood from the patient. After about 14 days, the trypanosomes will be found in the blood of the animal.

Xeno-diagnosis is carried out by allowing third-nymphal-stage clean laboratory-bred triatoma to feed on a patient and after an interval dissecting the bug and demonstrating the infection; this may well be considered too elaborate a procedure for an ordinary laboratory to carry out, as a long-established laboratory strain of triatoma must be used in order to obviate a false positive finding.

The Machado-Guerrero reaction is a form of complement-fixation test, in which an extract made from a heavily infected puppy's liver is used as antigen. A more recent modification is to prepare a more standardized antigen from cultures of *T. cruzi* in blood dextrose agar. The test is said to be specific to a high degree at any stage after the early acute stage; it is not usually positive before the 30th day. The result may however be positive in sleeping sickness and kala-azar; the latter disease occurs in South America.

PROGNOSIS

A high death rate is reported in the early acute stage in young children; the death rate is usually placed at about 50 per cent in the first year of life, but in the later age groups it declines rapidly. It must be remembered that this estimate takes into account only diagnosed cases, and, while it is possible that in young children the infection is always accompanied by marked symptoms, this is not the case in older children and adults, for many who give no history of an acute attack have been shown to be suffering from a chronic infection.

Though many cases have been discovered amongst persons showing no symptoms, the general indication is that the individual with a chronic infection is not on the whole a 'good life'.

PREVENTION

The dark corners and the thatched roofs of the huts of the poor obviously provide good cover for vectors; therefore any measure to improve the living conditions of the poor must be looked upon as a preventive procedure. Also, the bugs bite mostly at night, so that mosquito nets, even of very wide mesh, will give protection. Infants should certainly be so protected.

TREATMENT

None of the drugs so far used in the treatment of sleeping sickness has been of the slightest use in Chagas's disease.

Mazza has reported very good results with Bayer 7602, a preparation the composition of which has not been disclosed. The drug is given intramuscularly on alternate days, as a freshly prepared 3 per cent solution, in doses from 5 c.cm. for an adult; a total dosage of 0.222 gramme per kilogramme body-weight is considered to be sufficient to effect a cure. Brumpt also had good results with this drug, but not all other workers have been so successful.

REFERENCES

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|-------------------------|----|---|
| S. (1940) | .. | .. Chagas's Disease in San Juan. <i>Prensa Méd. Argentina</i> , 27 , 401. (Abstract— <i>Trop. Dis. Bull.</i> , 37 , 413.) |
| PACKCHANIYAN, A. (1939) | .. | .. Natural infection of <i>Triatoma gerstakeri</i> with <i>Trypanosoma cruzi</i> in Texas. <i>Pub. Health Rep.</i> , 54 , 1547. |
| <i>Idem</i> (1940) | .. | .. Experimental transmission of <i>Trypanosoma cruzi</i> infection in animals by <i>Triatoma sanguisuga ambigua</i> . <i>Pub. Health Rep.</i> , 55 , 1526. |
| YORKS, W. (1937) | .. | .. Chagas' Disease: A Critical Review. <i>Trop. Dis. Bull.</i> , 34 , 275. |

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TICK-BORNE RELAPSING FEVER

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Definition.—Relapsing fever is an acute specific disease occurring in many parts of the world, characterized by fever that appears in bouts of a few days' duration, with a sudden onset, a rapid subsidence, and a tendency to relapse at regular short intervals; it is caused by a spirochæte that is found in the blood and in other organs and tissues, and is transmitted to man by insects of at least two genera. The symptoms vary with the genus of the transmitting insect.

Discussion.—Relapsing fevers that comply with the above definition have been described in many temperate, sub-tropical and tropical countries. The causal organisms are morphologically indistinguishable from one another, but have been given a very large number of different names, both generic and specific. The following list has been prepared from data given by various workers :—

<i>Generic name</i>	<i>Specific name</i>	<i>Location</i>	<i>Insect vector</i>
<i>Spirochæta</i> <i>Spironema</i> <i>Treponema</i> <i>Borrelia</i>	<i>recurrentis</i>	Europe	} <i>Pediculus humanus.</i>
	<i>obermeieri</i>	Europe	
	<i>carteri</i>	India	
	<i>novyi</i>	America	
	<i>ægyptica (um)</i>	Egypt	
	<i>berbera (um)</i>	North Africa	
	<i>duttoni</i>	Central Africa	<i>Ornithodoros moubata.</i>
	<i>rossi</i>	East Africa	
	<i>kochi</i>	East Africa	<i>O. savignyi.</i>
	<i>crociduri</i>	Africa	<i>O. laborensis.</i>
	<i>persica (um)</i>	Persia and N. W. Africa	<i>O. papillipes.</i>
	<i>sogdiana (um)</i>	North Africa	<i>O. moubata, savignyi</i> and <i>erraticus.</i>
	<i>marocana (um)</i>	Morocco	<i>O. moubata</i> and <i>savignyi.</i>
	<i>hispanica (um)</i>	S. Spain	<i>O. marocanus.</i>
	<i>neotropicalis</i>	Panama	<i>O. talje.</i>
	<i>venezuelensis (e)</i>	Venezuela and Columbia	<i>O. venezuelensis.</i>
	<i>turicata</i>	Texas	<i>O. turicata.</i>
	<i>normandi</i>	North Africa	<i>O. moubata, savignyi</i> and <i>erraticus.</i>

The confusion in the generic names is due to natural conservatism on the part of the clinician, which is not surprising in the circumstances, and to disagreement on the part of the parasitologist, mainly on the issue of priority; there is no suggestion that there is more than one genus concerned.

The multiplicity of specific names, on the other hand, carries with it the implication that the disease is caused by a different species in each of the different countries in which it occurs; there is no justification for any such assumption. However, it seems probable that there are two species concerned, *Spirochæta recurrentis* and *Spirochæta duttoni*, which are the causal organisms of the louse-transmitted and the tick-transmitted relapsing fevers, respectively, and that all the other names are synonyms, *obermeieri*, *carteri*, *berbera*, *ægyptica*, and *novyi* for *recurrentis*, and the rest for *duttoni*. As well as their morphology, these two organisms have other common features, but there are many differences that seem to justify their distinction into two separate species. In the clinical syndromes as well as in the epidemiologies of the respective infections produced by the spirochaetes of these two species, there are marked differences, and they will be described separately.

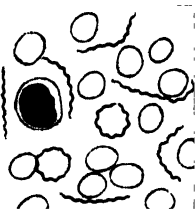


Figure 52 :
*Treponema
recurrentis*.

LOUSE-BORNE RELAPSING FEVER

Historical.—Rutty is given the credit for the first description of the disease in 1741, but up to the time of the 1843 Edinburgh epidemic—and probably later—the disease was confused with typhus (this was very natural as the two diseases so often appeared together in epidemic form), typhoid, bilious remittent malaria, and ‘putrid’ fevers; Craigie and Henderson described this epidemic in which for the first time the term ‘relapsing fever’ was used. Since this date there have been many epidemics in different parts of the world, very frequently in association with typhus epidemics; the dual nature of the epidemics was usually recognized, even before the causal organism was discovered.

EPIDEMIOLOGY

Geographical distribution.—Relapsing fever has occurred in epidemic form at some time or other in almost every country in the world. During the last twenty years or so, it has occurred in eastern Europe—Poland, Russia, and the Balkans; in Africa—in two belts divided by the Sahara desert, north Africa from Morocco to Egypt, and central Africa from Senegal to Abyssinia; and in Asia—Turkey, Syria, Iraq, India (except Bengal and Assam), China and Indo-China, Mongolia, and Asiatic Russia.

It seems probable that it does not occur in Australia or in the East Indies. Western Europe, with the exception of Ireland, has been free for some years, and no recent outbreak in America has been identified as louse-borne.

Epidemic features.—It is essentially an epidemic disease but cases that are apparently sporadic occur from time to time. Like most epidemic diseases it tends to occur in cycles; in this case the cycle has a 15 to 20-year periodicity. But it is certain that unnatural events such as wars, persecutions, poverty, and destitution, assist the natural events that determine the onset of the epidemics, e.g. the epidemic in eastern Europe and western Asia during and after the 1914–18 war.

Any country where the habits of the people are not naturally cleanly or where overcrowding and/or destitution are common is likely to suffer

epidemic outbreaks, and the disease is liable to spread to, and in, other countries and communities when normal standards are not maintained, during wars—amongst both troops and refugees—famines, and earthquakes and other natural disasters.

A severe epidemic occurred in the African epidemic belt south of the Sahara (*vide supra*) from 1921 for about eight years, and affected some millions of persons; the death rate is said to have been about 5 per cent of the populations of these countries, and in some it was as high as 25 per cent. In India, there has been little relapsing fever since 1929 when the last traces of the 1923-4-5 epidemic disappeared.

Epidemic relapsing fever is very frequently but not only always associated with epidemic typhus; in a mixed epidemic the latter usually predominates.

Seasonal incidence.—There is a distinct seasonal variation in incidence; the height of the epidemic wave is usually in the spring. In India and Iraq, the disease used to disappear completely during the hottest months of the year.

Age, sex, race, and occupation.—Relapsing fever appears to be most common in male adults, but persons of all ages and both sexes are susceptible. Individuals of all races are susceptible unless protected by previous experience of the disease; when a large percentage of the population is thus protected, racial immunity may be simulated.

Washermen or -women, and dealers in old clothes are particularly liable to be infected. Nurses and hospital attendants are also exposed through close contact with louse-infected patients, but not doctors, at least not to the same extent as in typhus, since viable spirochætes are not present in the dried faeces of lice, and there is therefore no air-borne infection.

ÆTIOLOGY

Historical.—Obermeier first found the parasite in 1868, but he did not describe it until about five years later. Lebert named it *Protomycetum recurrentis* in 1874, and Cohn *Spirillum obermeieri* in the next year; the specific name *recurrentis* thus has preference. Other workers in other countries, e.g. Vandyke Carter in India in 1876, found probably the same species of spirochæte and gave it different names. In 1907, Mackie showed that the louse was the important transmitter in India; his observations were confirmed and extended by Nicolle, Blaisot, and Conseil (1913) in north Africa, who showed that the transmission was not by the bite but by the crushing of the louse on the skin.

The causal organism. Morphology and staining.—*Spirochæta* recurrentis* is an actively motile spiral organism with five to ten fairly regular loose primary spirals; it is from 10 to 20 μ in length and about 0.2 μ in thickness; each spiral is 2 to 3 μ in length and 1 μ in amplitude. The spirochætes can be seen, though not accurately, in a fresh specimen of blood preferably by dark-ground illumination. They move by rapid

* The generic name *Spirochæta* is used here because it is still the most popular one. When parasitologists arrive at a unanimous decision as to the correct generic names, it will be time for clinicians to adopt them.

In the more recent classifications, there are no organisms pathogenic in man in the genus *Spirochæta*. The spirochætal organisms with which we are concerned in this book are four:—*Treponema (Borrelia) recurrentis* and/or *duttoni*, a flexible organism with fairly regular loose primary spirals, the cause of relapsing fever; *Treponema pertenue*, an organism with regular short spirals (morphologically indistinguishable from the causal organism of syphilis), the cause of yaws; *Treponema carateum (herrijoni)* another organism with short fairly regular spirals similar to the last-named, the cause of pinta; *Spirillum minus*, a short rigid organism with 3 or 4 short spirals and flagella at each end, the cause of rat-bite fever; and *Leptospira icterohæmorrhagiae*, a flexible organism with numerous tightly-wound primary spirals and a secondary characteristic hook, sometimes at each end, the cause of Weil's disease.

rotation, but not apparently purposefully, for they move backwards and forwards within the space of the microscopic field.

They stain well with all Romanowsky stains, and when stained assume various shapes, often a circular one in which the spiral waves are completely lost. The spirochæte appears very fine in the stained specimen and the ends taper off to invisibility, but there is no true flagellum (see plate II : H).

Culture.—The spirochætes can be grown anaerobically in a medium containing ascitic fluid, citrated blood, and kidney substance, but they do not grow well.

Distribution and pathogenesis.—They are found in the blood during the height of the febrile attack, but disappear just before the fall of the temperature, reappearing during the relapse. It has been suggested that during this period the spirochætes assume a granular form, since infection has been transmitted by blood taken during the afebrile phase; on the other hand, it has been shown that, during the remission, the spirochætes find their way into reticulo-endothelial cells in the internal organs, *e.g.* the spleen, and the brain, where they can be found as such.

Infection can be transmitted to a number of animals, *e.g.* monkeys, squirrels, rats, and mice, but not to rabbits or guinea-pigs. In monkeys the attack is very similar to that in man; 48 to 72 hours after the inoculation, a febrile attack occurs which lasts three or four days; there is a relapse after two to eight days, and the cycle may be repeated two or three times. In smaller animals, the organisms may appear in the blood in large numbers 24 hours after intraperitoneal inoculation of infected blood; relapses are less constant.

Immunity.—Immune bodies appear in the blood after an attack; they are capable of agglutinating and lysing homologous spirochætes and protecting animals against infection. The immunity does not last long. Immunity against *Spirochæta recurrentis* gives some but not very complete protection against infection with *Spirochæta duttoni*, and the antigenic relationship between these two species, if separate species they are, is of a much lower order than that between the various strains (or types) of *recurrentis* (*vide infra*).

To explain the phenomenon of relapse, it is suggested that the immune bodies appear in the blood and cause the spirochætes to disappear into the internal organs; these immune bodies are very transitory and when they disappear, the spirochætes return to the systemic blood, multiply, and again cause fever; more antibodies are formed; and so on, until the antibody load is sufficient to knock out the infection altogether.

In the writer's opinion, the more feasible explanation is that there is a multiplicity of strains with slightly differing antigenic structures, (*cf.* the antigenic structure of Flexner dysentery strains, *q. v.*), that when a person is infected, he is infected by a number of strains of which one is dominant and causes the first bout of fever; antibodies appear and suppress the spirochætes of this first strain; spirochætes of another strain, hitherto dormant, now appear and multiply; and so on, until eventually enough antibodies are formed to counteract spirochætes with all possible antigenic patterns. This hypothesis is supported by the work of Cunningham and others (1934, *et seq.*), in which he showed that in one individual the 'type' of spirochæte present in the initial attack was different from that present in the first relapse, and that, when a second relapse occurred, a third type appeared, and so on. The type recoverable during the apyrexial period was always the type that appeared in the *next* paroxysm. He separated

nine antigenic types (as he called them), four of which were stable types, maintaining their antigenic individuality through many sub-passages, but the other five tended eventually to revert to one or other of the four stable types.

Transmission.—This is effected by the louse, *Pediculus humanus*. After the louse has fed on an infected person, the spirochætes disappear in about 24 hours and are not traceable in the louse, nor is it infective for another three to five days; after this they reappear as slender metacyclic forms in the fluid of the body cavity of the louse and can be found in all parts of its body (they are easily demonstrated by taking off a leg and making a smear from the exuding fluid); the louse remains infective for the rest of its life. Transmission occurs when the louse is crushed and the body-cavity fluid rubbed into the abraded skin. *The bite of the louse does not transmit infection, nor do its fæces.* It is a question whether infection can be transmitted through the unbroken skin, by the blood or by a crushed louse; the balance of evidence suggests that it can. In 1918, during a relapsing fever epidemic, the writer lost (temporarily) a succession of louse-free post-mortem assistants from relapsing fever, though he himself escaped infection—by the strict use of rubber gloves, he believes. In these men small abrasions could not be excluded.

Source and spread of infection.—Whilst man is not the only susceptible mammal, the louse *Pediculus humanus* feeds only on man, so that man must always be the source of infection. It is however a possibility that the tick-borne spirochæte of endemic relapsing fever (*vide infra*) might provide the initial infection for a louse-borne epidemic. It has been shown that it is possible to infect lice with this organism, and it is conceivable that, after several passages through the louse, the spirochætal strain might undergo some biological change so that it behaves like, or actually becomes, *Spirochæta recurrentis*. The infection is spread by direct contact with the body of a louse-infected patient, by handling his louse-infected clothes, or by louse interchange during close contact, and it may be conveyed considerable distances in louse-infected clothes.

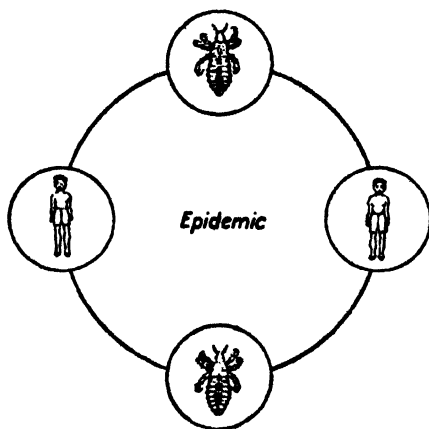


Figure 53 : The transmission cycle in louse-borne relapsing fever.

PATHOLOGY

Morbid anatomy.—The large majority of the patients who die from this condition, die from some secondary infection, and the true pathological picture is hard to gather.

In a severe case, the skin, internal organs, and mucous membranes are jaundiced and show numerous petechial hæmorrhages. The liver and spleen are usually enlarged.

The most constant lesions are in the spleen; this organ is enlarged and soft, and shows many miliary necrotic lesions, especially in the malpighian corpuscles.

In sections there will be seen areas of congestion and cell infiltration around the malpighian corpuscles, in which spirochætes will be found inside proliferating endothelial cells.

In the bone marrow there is marked leucoblastic hyperplasia.

In the other organs, in the liver and kidney, there is cloudy swelling and degeneration of the parenchyma cells.

Blood picture.—There is usually a distinct polymorphonuclear leucocytosis, with an actual increase in large mononuclears also. Counts of about 12,000 to 15,000 per c.mm. are usually found. This is not a constant finding.

Reference to the presence of the spirochæte in the blood has been made above (see also Diagnosis).

Urine.—Slight albuminuria will be found in more than half of the cases, and often granular casts; in severe cases there may be hæmaturia.

SYMPTOMATOLOGY

The incubation period is from three to seven days as a rule, the limits being from 2 to 14 days. (In experimental infections, it has always been between two and six days.)

The onset is sudden, sometimes with a rigor, the temperature rising to 104° or even higher in 24 hours; the pulse is rapid. There are often severe pains all over the body, suggesting dengue, but they are particularly severe in the calves; there is intense headache, with photophobia. The skin is hot and dry but occasionally there are attacks of sweating. The eyes show an icteric tinge. Epistaxis is common. The tongue is coated but usually moist, and constipation is constant. Bilious vomiting at the onset is not unusual, and may be a marked feature of some severe epidemics.

An erythematous rash appears early in the first febrile attack in perhaps less than half the cases. In severe cases this may become petechial and even hæmorrhagic. It appears to start from the tip of the mastoid process and it spreads out over the neck, shoulders, arms, back and chest.

Frank jaundice occurs in 20 to 50 per cent of cases in different epidemics: it appears early.

Both spleen and liver are enlarged in the majority of cases; the latter will usually be tender. The splenic enlargement is only slight and may disappear between attacks. The first attack usually lasts five or six days, but occasionally it will be prolonged even up to 12 days; the crisis then occurs and the patient's temperature drops to sub-normal, with profuse sweating and in severe cases with considerable prostration. Heart failure at this stage is not uncommon. Cases have been reported in which the temperature fell 10°F. in a few hours.

All the symptoms subside during the apyrexial period, but the patient will often be very weak; this remission period will last from four to nine days.



Figure 54 : Temperature chart in louse-borne relapsing fever (original).

Megaw takes the view that 'the disease period', that is the time from the onset of the first attack to the onset of the first relapse, is constant for each type of relapsing fever, but that the febrile and afebrile periods may vary reciprocally, so that, if the febrile period is prolonged, the afebrile period will be correspondingly shortened; in this form of relapsing fever, the disease period is from 12 to 16

days, average 13 days. This view is not universally accepted.

The first relapse is seldom as severe, or as long, as the initial attack, but is otherwise very similar to it. After another interval, usually shorter than the first, in the writer's experience, there may be a second relapse which will again be shorter and less severe than the first.

In this form of the disease there are never more than four relapses. The following figures have been given for the number of relapses that occur in different epidemics :—

A single attack	..	10 to 50	per cent.
One relapse	25 to 50	" "
Two relapses	10 to 40	" "
More than two relapses	1 to 2	" "

Complications and sequelæ.—Cough and bronchitis are so common in temperate climates that they may be looked upon as a constant feature of the disease. They are less common in the tropics. Broncho-pneumonia is a relatively common complication in cold climates.

In pregnant women, abortion will usually occur. Eye complications are not uncommon, particularly in a mal-nourished population; these include iritis and ophthalmia.

Parotitis, nephritis, polyarthrititis and neuritis are rarer sequelæ; the latter is very rare in this form of the disease, though common in tick-borne relapsing fever.

DIAGNOSIS

While the complete temperature chart of a case of relapsing fever is so characteristic that one could scarcely fail to recognize it, it must be remembered that one usually first sees the patient at an earlier date. The sudden onset of the fever, and the longer continuance than one would expect in malaria, and then the dramatic fall will help to distinguish the two diseases, but the microscope will have to be resorted to for confirmation.

In most epidemics, the parasites are easy to find, but are easily overlooked if not specifically looked for.

Giemsa's or Leishman's stains will show up the spirochætes very well. In looking for malaria parasites one focuses *on* the red cells and not *between* them, so that, unless one expects to find spirochætes, it is very easy to miss them even in a well-stained film. The curious circular form that they may take simulates a rather pale red cell, but, if one examines these forms carefully, the disguise is easily penetrated.

It should be remembered that the spirochætes disappear from the peripheral blood 24 hours before the crisis. They will not be found during the remission period, and are usually scantier in a relapse than in the initial attack.

Differential diagnosis.—At the height of the attack, influenza, dengue, malaria, yellow fever, Weil's disease, typhus and even small-pox may be suspected. The case showing a single attack may be mistaken for dengue, even in retrospect; the pulse after dengue is however usually very slow.

PREVENTION

Preventive measures will consist in keeping the populations in a louse-free condition, in preventing conditions that will encourage an interchange of lice (*e.g.* overcrowding), in the early hospitalization and treatment of all cases, and in instituting special measures for delousing all patients admitted to hospital during an epidemic.

Established lousiness will never be tolerated by an educated and sane individual, in ordinary circumstances, and its prevention is solely a matter of personal cleanliness.

The clothing of hospital and ambulance personnel should be white, one-piece, and with no openings in front (figure 55); gloves and gum-boots should be worn and the sleeves and trousers tied firmly round the wrists and ankles, a white handkerchief tied round the head, covering the hair, and a gauze mask worn across the mouth and nose. For those dealing with heavily infected clothes, a respirator that also covers the eyes would be a desirable additional safeguard; this last precaution is even more important where typhus is also suspected. For hospital personnel, the best protection that can be given is the complete delousing of the patients before admission.

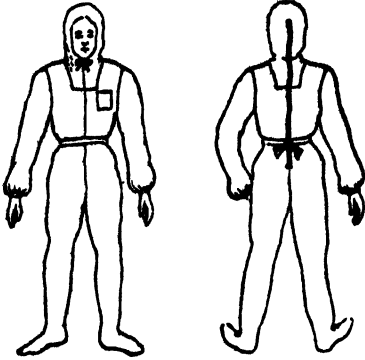


Figure 55 : Figure shows one-piece suit for use by hospital and ambulance personnel. It is closed by means of a zipper behind, elastic round the wrists, and a tape round the face, tied under the chin.

Delousing hospital admissions.—With a little organization, this can be effected more easily than where one is dealing with a population that has to be reclothed; it will however necessitate complete removal of all hair from the body, and, in the case of men, it will be advisable to include the head, followed by thorough washing with antiseptic soap under supervision. Women will usually object to having their heads shaved, and an elaborate process of hair washing is necessary.

The old method of effecting this was by saturating the hair in 1 in 40 carbolic acid and tying the head up in a towel for about 2 hours; after this it is washed, and then a hair lotion rubbed in; for the latter purpose, a good mixture is :—

Kerosene	..	50 per cent.	Citronella oil	..	1 per cent.
Tar oil	..	5 „ „	Coconut oil	..	44 „ „

Coconut oil alone will not destroy lice, though it may gum up the ova and prevent hatching to some extent.

A much more effective method, of which the writer has had recent first-hand experience, is by spraying the hair thoroughly with a pyrethrum and kerosene mixture. The patient should be given a small towel to hold over her face; the hair is then sprayed thoroughly from all directions with a no. 15 de Vilbiss atomizer, care being taken that the lotion reaches all the roots of the hairs.

The lotion is made with one part of 'pyroicide 20', or any other concentrated pyrethrum extract, and 19 parts of white kerosene or deobase oil which is scentless. To this a little (one per cent) of citronella oil may be added to give the lotion a smell, but it is not necessary.

Underclothing removed can be disinfected in 2 per cent cresol or lysol, and other clothing autoclaved. Outer garments should be sterilized by autoclaving; a comparatively low temperature of 60°C. maintained for 10 minutes will kill lice and their eggs. Fumigation will be necessary for boots and other clothing that would be spoilt by heat or washing; exposure for 2 hours to 0.2 per cent cyanogas is in most circumstances sufficient for this.

Repeated inspection of the clothing of personnel, especially the menial personnel, of a hospital is an essential measure to maintain freedom from lice. A lens will facilitate the search for lice and their eggs; special attention should be paid to the seams of the underclothing. The head should also be inspected; the empty shells of ova are easily seen when they have been carried away from the scalp by the growth of the hair, but the living ovum, or nit, lies closer to the scalp and may be difficult to detect.

For the delousing of troops or infested populations, a very well-organized delousing station is necessary. This must include an entrance room for undressing, with side rooms for dirty underclothes, the disinfection of outer clothing, and the safe-keeping of money and other valuables; from this room the individual passes through the barber's room, the washing room, and the medical-inspection room to the dressing room where he is issued with clean under-linen, and receives back his outer clothing and valuables.

TREATMENT

The general and dietetic treatment will be that of any short febrile disease. It is not necessary to force food during the febrile period, but a fluid diet of about 1,000 calories with plenty of additional fluid will be sufficient. The calorie intake may be doubled during the intermission, but the patient should not be given the free run of his teeth during this period, as he may be ravenously hungry. The diet at this time should be well balanced and still mainly fluid.

Rest in bed is important; it will be observed naturally during the febrile attacks, but the patient should be warned seriously of the danger of collapse and heart failure during the early intermission period.

Mouth sanitation should be given special attention.

Specific treatment.—The arsphenamine preparations have a rapid specific action. Novarsenobillon has proved the best drug in the writer's experience, but any of the well-known preparations can be used. A single dose of 0.6 gramme for a normal male adult, and a smaller dose in others on the basis of about 0.01 gramme per kilogramme body-weight should be given; a second dose is seldom necessary and should only be given if a relapse occurs.

If treatment cannot be given within the first three or four days of the onset, and the state of the patient is not obviously critical, it will be as well to withhold the specific treatment, since, if the injection is given just before the crisis, it may dangerously enhance the collapse that sometimes follows the crisis; further, as in some epidemics in more than half the cases no relapse occurs, it may be possible to dispense with the specific treatment altogether. This may be important in an epidemic when cost and/or the supply of drugs have to be considered; arsphenamine can in such circumstances be reserved for severe cases only.

Stovarsol, six 0.25 g. tablets daily, is recommended, if parenteral arsphenamine is contra-indicated for any reason. German workers have recommended gold preparations, *e.g.* solganal B. & A. 69.

PROGNOSIS

After one adequate dose of arsphenamine the relapse incidence will not exceed 15 per cent.

The death rate varies very considerably from epidemic to epidemic, and according to the circumstances. Figures from 1 to 50 per cent are quoted, but the latter high figure would only occur in a starved or exhausted population.

TICK-BORNE RELAPSING FEVER

Historical.—Livingstone suggested that relapsing fever in Africa was conveyed by ticks. A number of workers described the finding of the spirochæte in African cases, but it was Dutton and Todd in 1905 who definitely showed that infection was transmitted by the tick, *Ornithodoros moubata*.

Later, other workers discovered other transmitters of the disease in other countries (see p. 224).

EPIDEMIOLOGY

Geographical distribution.—This form of the disease has a typically tropical and sub-tropical distribution. It is found in southern Spain, north Africa including Morocco, north-west Africa, east Africa, and central Africa; in Iran and neighbouring countries and in northern India; in central and south America, Panama, Columbia and Venezuela, Peru, Uruguay, Brazil and Argentina; in Mexico and a number of southern and eastern states of the U.S.A., California, Colorado, Arizona, Texas, and Kansas.

Epidemic features.—It is essentially an endemic disease and it occurs sporadically in the countries mentioned above. Children are very likely to be infected whilst playing on the ground, as thereby they come into closer contact with the ticks. It is a regional, or even a house infection; a history of a succession of infections amongst visitors to a house has often been obtained.

Temperature is an important factor controlling the development of the spirochæte in the tick. In tropical countries, the disease is perennial, but in the sub-tropics, cases occur mainly in the spring and summer, when the ticks are always most active.

ÆTIOLOGY

The causal organism, as has been stated above, is morphologically identical with *Spirocheta recurrentis*.

Transmission.—It is believed by some workers that *S. duttoni* was originally a parasite of *Ornithodoros moubata* and that man was only

infected incidentally; there is evidence that once infected, *O. moubata* is capable of maintaining the infection through many generations, if not indefinitely, and transmitting it to man, so that the cycle of infection is as shown in figure 56. However, clean ticks may become infected through feeding on an infected man. The spirochætes are taken into the insect's gut with the blood meal; after disappearing for a few days, they

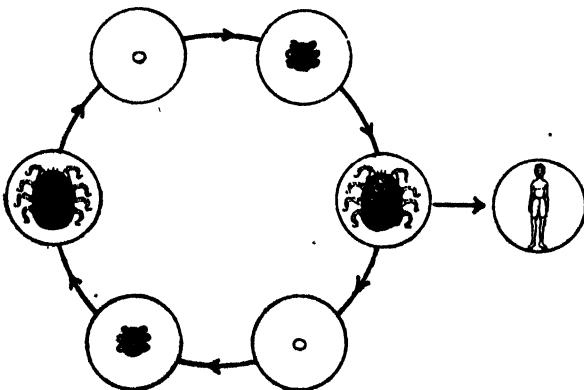


Figure 56: The transmission cycle in African (*moubata*) tick-borne relapsing fever.

reappear and invade practically all the tissues of the insect host. They are found in large numbers in the body-cavity fluid, where they multiply. The

spirochaetes enter the body cells, including the cells of the ovaries, and are transmitted to the next generation through the ovum.

In the case of the other vector ticks, *Ornithodoros erraticus*, for example, the infection dies out after passing through two or three generations, and

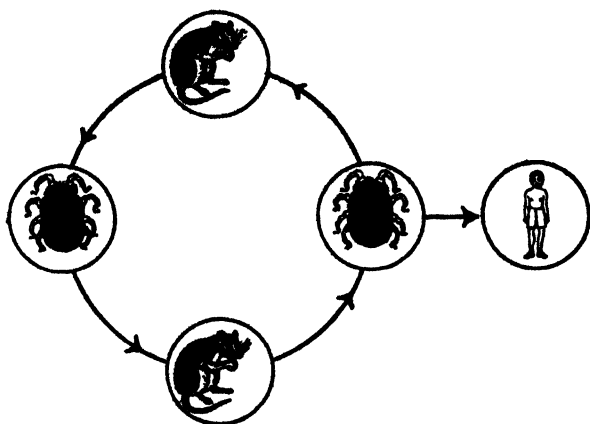


Figure 57: The transmission cycle in other tick-borne (e.g. *erraticus*) relapsing fevers.

the tick only becomes reinfected after feeding on an infected mammal. Unlike *O. moubata*, that feeds on man only, these other ticks feed on their natural hosts, rodents and small carnivores, which act as reservoirs of infection, and they transmit the infection to man sporadically (see figure 57).

The actual method of transmission is a matter of controversy, but, as diverse results have been obtained by reliable workers using different vectors, it is more

than probable that there are a number of ways in which transmission may be effected. The three probable methods are *via* the salivary glands and/or contaminated mouth parts during the process of feeding, by the coxal fluid, and by the excreta. It seems probable that with so many vectors, transmission will take place by each one of the three methods, and that with some ticks transmission will be by more than one method, possibly by all three; Buxton (1939) believes that in *O. moubata* the coxal fluid is the only medium of infection. It seems very unlikely that, in nature, transmission would take place by the tick being crushed on the skin; ticks are far too tough for this, though experimentally it is possible to cause infection in this way.

Animal reservoirs.—Vector ticks other than *O. moubata* feed normally on wild rodents and small carnivores, e.g. rats, mice, gerbilles, weasels, foxes, and armadillos, which act as reservoirs of infection. Dogs have been found naturally infected, and *Rhipicephalus sanguineus*, the dog tick, transmits the infection from the dog to man. Infection can also be acquired by picking ticks off infected dogs.

PATHOLOGY

The pathological lesions are very much the same as in louse-borne relapsing fever, but this spirochaete shows a greater tendency to attack nerve tissue. In experimental infections in mice, the spirochaetes can always be recovered from the brain; the clinical evidence of this neurotropism is the frequency with which neuritis and paralysis occur as a sequel.

The blood picture is the same as in the louse-borne infection; the spirochaetes are usually scantier, and the thick-drop method may have to be adopted to find them. A positive Wassermann reaction appears to occur in this disease in 10 to 20 per cent of cases, irrespective of syphilitic infection.

SYMPTOMATOLOGY

In each different relapsing-fever area, the disease shows a somewhat different picture; only the special features of the various types, as they

differ from the louse-borne infection, as well as from one another, will be indicated.

The special features of the African type are :—

The incubation period tends to be slightly longer, seven to ten days; the febrile period may be much shorter, lasting only a day or so, but in some

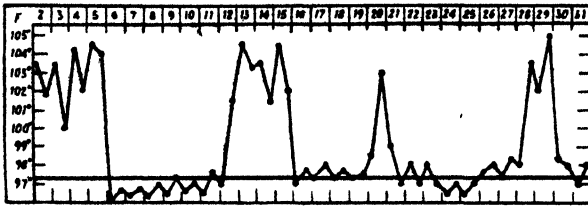


Figure 58 : Temperature chart in tick-borne relapsing fever (original).

(‘afebrile’ period) seldom remains quite normal but is irregular, frequently rising to 99.5°F. or 100°F. Occasionally, the fever loses all its relapsing character and becomes intermittent.

The relapses are far more numerous; as many as eleven have been reported.

In some outbreaks, fulminating cases occur in which there is severe jaundice, hæmorrhages, and coma, and the patient dies within 48 hours.

The common complications are bronchitis and pneumonia, as in the other forms of relapsing fever, but in tick relapsing fever, the special sequelæ are diarrhœa and dysentery, neuritis, spastic paralyses, aphasia, strabismus, deafness, hemiplegia, and, fortunately very rarely, atrophy of the optic nerve. Parotitis and iritis also occur. The cerebrospinal fluid may be under increased pressure; in it, spirochætes are sometimes found, and there is usually an increase of lymphocytes.

In the Iranian type the disease is milder, the initial pyrexial bout usually lasts four or five days, there may be deep remissions, and there are a number, usually four or five, relapses of much shorter duration, not usually more than three days. The attack is usually relatively mild, but severe attacks have been reported.

The Spanish type is also mild, but the patient is very drowsy, and prostration may be considerable when the temperature falls. Herpes labialis is common. The spleen and cervical lymphatic glands are enlarged.

There are not usually more than four relapses.

The leucocytosis occasionally amounts to 25,000 per c.mm..

DIAGNOSIS

The clinical diagnosis will be more difficult than in louse-borne relapsing fever, and the fever will often simulate malaria. The spirochætes also may be more difficult to find in the blood film, and thick films should be examined (see p. 87), but animals are more easily infected with *Spirochata duttoni* than with *Spirochata recurrentis*; in mice the brain should be examined for spirochætes.

PREVENTION

The preventive measures to be adopted against this disease must obviously be very different from those employed against the louse-borne infection; however, the possibility that the spirochæte may change its ‘tropism’ and become adapted to living in the louse should not be forgotten,

and lousiness should be looked upon as particularly dangerous in an endemic area of tick-borne relapsing fever. It is possible to institute some measures against *Ornithodoros moubata*, because they live mainly in the walls and floors of native huts and even European houses. Old heavily infected huts or houses should be demolished, preferably by burning, and replaced by buildings with concrete floors and well-built brick walls. Other houses it may be possible to repair and to make tick proof.

The sites of camps must be carefully selected, and old camp sites and areas near villages avoided.

Sleeping on the floor should be discouraged, but old locally-made beds should be avoided.

In the case of other tick vectors, preventive measures will be difficult, since they live in the caves and burrows of their alternative hosts and only come into man's habitations fortuitously. The control of domestic animals that may bring them in will be an important preventive measure.

For personal protection, suitable clothing that will protect from ticks, should be worn in 'tick country'. After walking in bush or jungle, the legs should be examined, any adhering ticks removed carefully, and the area from where they have been removed washed with a strong antiseptic. The starved tick does not transmit infection for some hours. The tick must not be pulled off, but touched with a hot cigarette end or some strong insecticide to make it loosen its grip.

TREATMENT

This is not materially different from that of the louse-borne relapsing type (*q.v.*). However, since in most of the tick-borne types, relapses are far more numerous, specific treatment will be indicated whenever it is available. The infection is more resistant to treatment, and the injections will often have to be repeated.

PROGNOSIS

The average death rate is about 6 per cent. Some types are very mild, but from time to time a fulminating outbreak of the African type occurs, with a death rate of at least 50 per cent.

REFERENCES

- BUXTON, P. A. (1939) *The Louse*. Edward Arnold and Co., London.
- CUNNINGHAM, J., THEODORE, J. H., and FRASER, A. G. L. (1934). Further Observations on Indian Relapsing Fever. *Indian J. Med. Res.*, **22**, 105 and 595; **24**, 571 and 581.
- DUTTON, J. E., and TODD, J. L. (1905). The Nature of Human Tick-fever in the Eastern Part of the Congo Free State. *Liverpool School Trop. Med. Mem.*, No. 17. University Press of Liverpool.
- MACKIE, F. P. (1907) The Part played by *Pediculus corporis* in the Transmission of Relapsing Fever. *Brit. Med. J.*, **ii**, 1706.
- NICOLLE, C., BLAIZOT, L., and CONSEIL, E. (1913). Etiologie de la Fièvre Récurrente son mode de Transmission par les Poux. *Ann. Inst. Pasteur*, **27**, 204.

RAT-BITE FEVER

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Definition.—Rat-bite fever is a fever of relapsing type, caused by micro-organisms that are conveyed to man by the bite of small animals, mainly rats.

Discussion.—All recent evidence suggests that the parasite principally responsible for this disease is the spirochætal micro-organism *Spirillum*

minus. However, the careful work of Schottmüller (1914) and others who found *Streptobacillus moniliformis* in animals inoculated with the blood of patients suffering from a post-rat-bite fever cannot be ignored, and recent work in the United States suggests that it may be the commoner causal organism in temperate climates (Brown and Nunemaker, 1942). Knowles and Das Gupta (1928) once isolated a streptobacillus in a case of rat-bite fever in which they had already isolated *Spirillum minus*; in practically every other case they found the latter organism, and from this they concluded that, in India at least, *Spirillum minus* is the sole causal organism and that the presence of a streptobacillus was an accidental association. The disease caused by *Spirillum minus* will be described here.

Historical.—The disease has been recognized, in Japan and elsewhere, as a clinical entity for many years; in Japan it was known as *sodoku* (so = rat; doku = poison). In India, the first clinical record was in 1913. However, the discovery in 1916, by Futaki and others, of the causal organism gave the disease a more concrete form.

EPIDEMIOLOGY

Geographical distribution.—This is probably world-wide, but the tropical association of the disease is not solely a matter of poor sanitary and social conditions; though these undoubtedly play an important part, climate *per se* is probably a factor. Most of the earliest cases were reported from Japan. Knowles and Das Gupta (1928) drew attention to the fact that it was a common disease in India and certainly in Calcutta, and the subsequent annual reports of the School of Tropical Medicine have borne this out; between 50 and 100 cases are seen annually at the out-patient department of the School.

Isolated cases have been reported from many countries. The first definite report of a case in the United States was made by Shattuck and Theiler in 1924, and Bayne-Jones (1931) collected 75 apparently authentic cases from the literature; *Spirillum minus* had been isolated in only five of these cases.

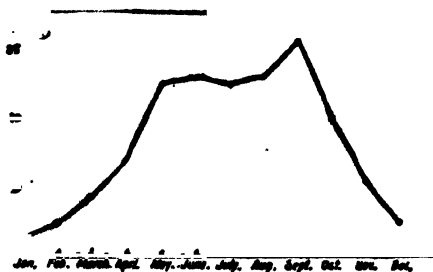


Figure 59 : Seasonal incidence of 455 cases of rat-bite fever in Calcutta between 1931 and 1936.

(Chopra, Basu and Sen, 1939.)

Epidemic features.—It is essentially a sporadic disease; it occurs in those living under insanitary conditions and most subject to the bites of rats; the published records of age and sex incidence reflect only the age distribution of the population from which they are drawn; but there appears to be a definite seasonal incidence, which in Calcutta corresponds to the warm and humid months of the year (see figure 59).

ÆTIOLOGY

Historical.—The causal organism was first reported upon by Vandyke Carter in 1887 in India; he found it in the blood of rats, but did not associate it with the disease. Others reported a similar organism found in other rodents, but Futaki *et al.* (1916) were the first to associate it with the disease and isolate it from an infected patient. They named it *Spirochaeta morsus muris*. The organism differs from the true spirochaetes in possessing flagella, and its correct name is *Spirillum minus*. [The streptobacillus isolated by Schottmüller (1914) and later by others (*vide supra*) cannot, in the opinion of Topley and Wilson (1938), be ignored as the possible cause of a similar form of fever, but the *Spirillum minus* infection undoubtedly has a more tropical distribution.]

The causal organism.—*Spirillum minus* is a short, rigid, spiral organism measuring from 2 to 5 μ , but is occasionally longer, even up to 10 μ ; it is relatively thicker than the spirochætes; and the coils vary in number according to the size of the spirillum, but the length of each coil is uniformly about 1 μ . With dark-ground illumination, the rapid, darting, and progressive movements of the organism can be studied; these movements are effected by means of terminal flagella—of which there are several at each pole—and are very different from the backward-and-forward movements of the spirochætes. Multiplication takes place by transverse division.

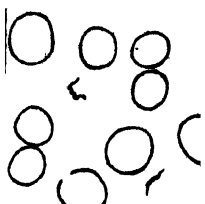


Figure 60 :
Spirillum minus.

The spirillum stains well with Giemsa's or other Romanowsky stains, but for demonstrating the flagella, Tribondeau's modification of Fontana's silver impregnation method is perhaps the best. The spirilla can be shown in the tissues by this method.

Cultivation of the organisms has been claimed by Futaki and others, but it is not at present a practical procedure.

The infection is readily transmissible to laboratory animals, monkeys, guinea-pigs, rats, and mice; the last-named are most commonly used. It has been claimed that the infection is transmitted from the mother to the young, either by intra-uterine or by milk infection. Das Gupta (1938) however failed to confirm this observation, as also to infect mice by feeding them on contaminated food. Nevertheless, it is not uncommon for one's whole stock of laboratory mice to become infected naturally.

Distribution in the tissues.—In man, the spirillum is found in the local tissues at the site of the bite, in the lymphatics draining the area, in the lymph nodes on the course of these, and in the blood. It has also been demonstrated in the liver, spleen, kidney and suprarenals.

In animals, it appears in the blood in about six days, and it has a predilection for the connective tissues of the nose, the lips, and the gums. Infection of the conjunctival sac is apparently common, the organisms being found in the secretions. *The salivary glands are not infected.*

Transmission.—This is effected by the bite of an infected rat or other small animal. The tissues around the mouth are particularly rich in spirilla, and when a rat bites viciously it usually damages its gums so that they bleed; this infected blood contaminates the wound. Another suggestion is that the mouth of the rat is infected by the conjunctival secretions that come down the nasal duct.

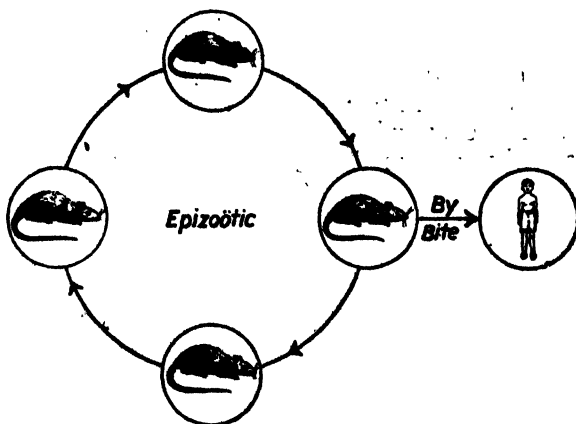


Figure 61 : The transmission cycle in rat-bite fever.

Animal reservoirs of infection.—Wild rats constitute the main reservoir; 3 per cent of wild rats in Japan have been shown to be infected. In

Animal reservoirs of infection.—Wild rats constitute the main reservoir; 3 per cent of wild rats in Japan have been shown to be infected. In

Calcutta, infected rats have frequently been found. After the rat, the cat is the most common agent of infection, and instances have been reported of a similar disease following the bites of weasels, ferrets, squirrels (Das Gupta, 1942), and even dogs; it will be noted that most of these are carnivores that habitually kill rats and are likely to have been infected by rats when they were killing them. As infection is apparently not transmissible by the oral route, it is uncertain how it is transmitted from rat to rat.

PATHOLOGY

Locally, there is hyperæmia and œdema of the skin and subcutaneous tissues, with polymorphonuclear and eosinophil infiltration. Similar changes will be found in the lymph nodes that drain the area.

There are few records of post-mortem examinations in man. Hyperæmia and œdema of the kidney, with degenerative changes in the tubular epithelium, and cloudy swelling and necrosis of the parenchyma cells in the centre of the liver lobules, have been described.

In the rat, there appears to be little tissue reaction to the infection. The liver may show some congestion. In mice, there may be conjunctivitis and loss of hair. Young guinea-pigs usually show emaciation, keratosis, and other eye complications, and die within two months.

Blood picture.—There is an increasing anæmia if the disease is allowed to progress untreated, but this is not very evident in cases in which treatment is instituted early. With the onset of fever, there is a sharp rise in the leucocyte count, which subsides during the remission periods; there is a relative increase in eosinophils, and a decrease in lymphocytes.

Urine.—A cloud of albumin is common and, more rarely, granular casts appear.

The Wassermann reaction is reported to be positive in this disease. Our experience in Calcutta contradicts this. Das Gupta chose Wassermann-negative volunteers and infected them experimentally with *Spirillum minus*; at no stage of the infection did their Wassermann reactions become positive. Other reports indicate that the Kahn reaction is frequently positive even when the Wassermann reaction is negative; the writer has recently confirmed this observation.

SYMPTOMATOLOGY

A definite history of a rat bite may be given, but, as the majority of bites occur at night, much more frequently the patient says that he was awakened by a sudden pain in his foot or hand, and that next morning he found an inflamed local lesion which was obviously a bite.

The incubation period is very variable, but the average is about two weeks; instances as short as three days and as long as several months have been reported. The initial lesions made by the bite may heal in a few days; this will depend on the degree of sepsis. Then, after the incubation period, the true onset will occur suddenly with a high rise of temperature and often a rigor, headache, pains in the joints and muscles, and a considerable degree of prostration. With the first and sometimes with each subsequent febrile paroxysm, there is a local response of the allergic type, with redness, swelling and œdema at the site of the original lesion, and, if this has not healed, there will be an increase in the amount

of discharge. The reaction may also occur in the proximal lymph nodes, which were possibly swollen previously but had meanwhile subsided.

At the same time a rash may appear on different parts of the body, mainly on the limbs and the trunk, but sometimes on the face, and rarely on the mucous membranes. The rash takes the form of large reddish-purple patches, as much as an inch to two inches in diameter; they are sometimes raised very slightly above the surface, but they would usually be described as macules. Sometimes purplish papules also appear. The rash subsides with the temperature and occasionally, but not usually, reappears during the relapses.

The rash is by no means common; it occurs in less than 2 per cent of our Calcutta cases.

The fever rises sharply to 103° or 104°F. and may remain as a high remittent temperature for three or four days; it then falls to normal within a

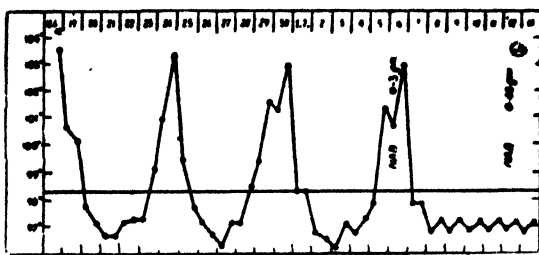


Figure 62 : 'Rat-bite' fever after a bite by a squirrel. (Das Gupta, 1942.)

A classical temperature chart of rat-bite fever showing regular periodicity and response to arsphenamine.

few hours, where it remains for a variable period but not usually more than a week (*see* figure 62). The second rise of temperature is usually as high as the first but the duration is shorter; if no specific treatment is given, these relapses may occur at intervals of from 6 to 10 days for many months, but, as a rule, the febrile paroxysms become less and less in height and duration, and eventually the infection disappears spontaneously.

The rhythm of the paroxysms may be disturbed by sepsis, and the temperature may show a moderately high, irregular curve in which the paroxysms are scarcely distinguishable (*see* figure 63).

DIAGNOSIS

A clinical diagnosis can often be made on the history alone; definite or circumstantial evidence of a rat bite which healed in a few days, an interval of about a fortnight, and a sudden attack of fever with a focal reaction, even before the relapsing nature of the fever with its characteristic periodicity (longer than malaria and shorter than relapsing fever) becomes apparent, are sufficient to establish a diagnosis with a considerable degree of certainty.

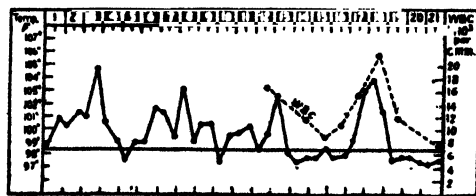


Figure 63 : Temperature chart and leucocyte count in rat-bite fever.

There are three practical laboratory methods of confirming the diagnosis: (a) by direct examination of serous exudate taken from the initial lesion, (b) by the immobilization test with the patient's serum and (c) by animal inoculation with exudate or blood.

(a) **Examination of local lesion.**—The hyperæmic or œdematous area around the site of the bite is pricked with a sterile needle, after sterilization

of the area and subsequent washing with normal saline, and the exudate is taken up with a capillary pipette and examined by dark-ground illumination. At first the darting movements of the spirillum make it impossible to identify it, but, if the specimen is sealed with paraffin or vaseline, left for a time, and examined later, the spirillum will easily be recognized by its characteristic shape, as well as by its movements, now slowed down.

Films made from the exudate stained by Leishman's or Giemsa's stains will often show the spirilla quite well, but Tribondeau's modification of Fontana's stain gives the best results; the technique of this method is described by Das Gupta (1938) as follows :—

(i) A thin film of the clear serous exudate is prepared from the lesion on a clean slide and allowed to dry in the air.

(ii) The slide is then laid on a staining-rack and flooded with Ruge's solution, which has the following composition : glacial acetic acid, 1 c.cm.; solution of formaldehyde, 2 c.cm.; and distilled water, 100 c.cm. The fixative is poured on and drained off; this is repeated two or three times for about a minute.

(iii) The fixative is drained off the slide, which is next covered with methyl alcohol and flamed by applying a lighted match. This completes fixation.

(iv) The slide is laid on the staining-rack and flooded with the following mordant : tannic acid, 5 grammes, in distilled water, 100 c.cm. It is gently warmed until steam rises. The best and least messy way of doing this is to wrap a little cotton-wool round the end of a piece of wire, soak it in alcohol, light it, and hold under the slide. When steam rises from the slide, the flame is removed and the mordant allowed to act for thirty seconds longer without further heating.

(v) The slide is washed with distilled water and then covered with Fontana's silver solution. To prepare this, a 5 per cent aqueous solution of silver nitrate is taken in a glass cylinder which has previously been thoroughly washed with distilled water. With a capillary pipette, a strong solution of ammonia is added drop by drop. A sepia precipitate forms and then re-dissolves. To the now clear solution more silver nitrate solution is added very carefully, and only drop by drop, from a capillary pipette, until a solution results which is just opalescent (and not more) on shaking. Not a drop more of the silver solution should be added than is necessary to produce slight opalescence. The slide is covered with the solution and warmed gently until steam rises; then the flame is removed, and the warm solution is allowed to act for a further thirty seconds.

(vi) The film is washed in distilled water and allowed to dry in the air. It should never be blotted.

The film is then examined with an oil-immersion lens. The spirilla are stained an intense brown-black or black against a faint yellow background.

The spirilla are usually scanty and a determined search for them has to be made: they were found in 64 per cent of our Calcutta cases believed on clinical grounds to be cases of rat-bite fever.

(b) Immobilization of spirilla with patient's serum.—Blood is taken from an infected mouse's tail and mixed with a 1-in-5 dilution of the patient's serum in normal saline. A coverslip is applied and the specimen sealed with vaseline. Examined after an hour, the spirilla will be immobile if the patient is suffering from rat-bite fever; but still very active in the control (with normal serum); a control must always be put up. A positive result definitely indicates rat-bite fever; a negative result does not exclude this diagnosis.

(c) Animal inoculation.—The most suitable animals are :—(i) *White mice* : the limitation is that those animals are very subject to 'natural' infection, so that clean stock has to be used and the mice examined thoroughly before inoculation. (ii) *Young guinea-pigs* : in these the development of the infection is slower and perhaps less certain. (iii) *Other animals* : these include adult guinea-pigs, rabbits and monkeys.

The inoculation is made either from the serous exudate from the lesions, a drop of which is given subcutaneously, or from the blood, 0.5 c.cm. being given intraperitoneally to a mouse, 1 c.cm. to a young guinea-pig, and 2 c.cm. or more to any of the larger animals used.

The blood of the animals is examined from the sixth day onwards, by cutting off the tip of the mouse's tail, or in the case of the guinea-pig by snipping its nail or puncturing a vein in its ear. The blood is placed on a carefully cleaned thin slide, covered with a clean coverslip, ringed with vaseline, and left for half an hour; at the end of this time, it is examined with dark-ground illumination. The motile spirilla will be identified easily.

Spirilla were identified in 70 per cent of our clinically typical Calcutta cases by blood inoculation into white mice.

Therapeutic test.—One adequate dose of arsphenamine will always interrupt, at any rate temporarily, the periodicity of the fever.

Differential diagnosis.—The conditions likely to be confused with rat-bite fever are :—

(i) Septic fever from the bite : this will usually follow the bite almost immediately.

(ii) Filarial lymphangitis and fever : microfilariae will usually be found in the blood taken at night.

(iii) Relapsing fever : the 'disease period' is usually much longer, and spirochætes will be found in the blood.

(iv) Malaria : the periodicity is much shorter, malaria parasites will be found in the blood, and the fever will respond to anti-malarial drugs.

Rat-bite fever may simulate other short febrile diseases, such as dengue, sand-fly fever, and influenza, but the diagnosis will be cleared up when the characteristic periodicity of the fever becomes apparent.

TREATMENT

The prophylactic treatment of a rat bite consists in applying pure phenol to the wound with a match-stick swab, washing this out with sterile water, putting powdered sulphanilamide into the wound, and applying a dressing.

Specific treatment is provided by any of the arsphenamine group of drugs, given according to the weight of the patient (see p. 232). Usually two injections will effect a complete cure, but it may be advisable to give a third.

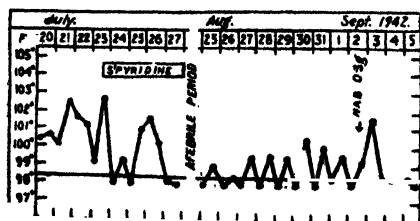


Figure 64 : Sulphapyridine appeared to effect a cure but *Spirillum minus* was still present in the blood and the fever relapsed.

Sulphapyridine given in the usual doses appears to control the fever temporarily in some cases, but it does not effect a cure. In the case of which the temperature chart is shown in figure 64 spirilla were found in the blood until novarsenobillon was given.

PROGNOSIS

If adequate treatment is given, complete recovery may be expected by the time the local lesion settles down, and the death rate in our experience has been negligible. In Japan, however, a death rate of 10 per cent has been reported.

REFERENCES

- BAYNE-JONES, S. (1931) .. Rat-bite Fever in United States. *Internat. Clin.*, **3**, 235.
- BROWN, T. McP., and NUNEMAKER, J. C. (1942). Rat-Bite Fever: A Review of the American Cases with Reevaluation of Etiology; Report of Cases. *Bull. Johns Hopkins Hosp.*, **70**, 201.
- CHOPRA, R. N., BASU, B. C., and SEN, S. (1939). Rat-Bite Fever in Calcutta. *Indian Med. Gaz.*, **74**, 449.
- DAS GUPTA, B. M. (1938) .. Experiments on the spirillum of rat-bite fever. *Indian Med. Gaz.*, **73**, 14.
- Idem (1942) .. *Spirillum minus* infection acquired from an Indian squirrel (*Sciurus sp.*). *Indian Med. Gaz.*, **77**, 541.
- FUTAKI, K., TAKAKI, F., TANIGUCHI, T., and OSUMI, S. (1916). The cause of rat-bite fever. *J. Exper. Med.*, **23**, 249.
- KNOWLES, R., and DAS GUPTA, B. M. (1928). Rat-bite fever as an Indian disease. *Indian Med. Gaz.*, **63**, 493.
- Row, R. (1922) .. Some cutaneous manifestations in rat-bite spirochaetosis. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **16**, 203.
- SCHOTTMULLER, H. (1914) .. Zur Ätiologie und Klinik der Bisskrankheit. *Dermat. Woch.*, **58**, 77. (Abstract—*Trop. Dis. Bull.*, **4**, 162.)
- SHATTUCK, G. C., and THEILER, M. (1924). Rat-bite Disease in the United States with Report of a Case. *Amer. J. Trop. Med.*, **4**, 453.
- TOPLEY, W. W. C., and WILSON, G. S. (1938). *The Principles of Bacteriology and Immunity*. Edward Arnold and Co., London.

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Introduction.—Under the general name 'leptospirosis' are grouped together a number of diseases that have many common clinical and pathological features, and which are caused by organisms of the genus *Leptospira*; of these the best known is Weil's disease or infective jaundice, another is the seven-day fever of Japan, but there are probably many other similar but distinguishable syndromes which are as yet not clearly differentiated.

Leptospira is the generic name of a group of spirochæte-like organisms; they have tightly-wound spirals, which give them the appearance of a twisted rope, and, usually, hooked ends. They live saprophytically as well as parasitically. The commonest species is *Leptospira biflexa*, which is found in water supplies in many parts of the world and is a filter-passer. The parasitic species infect rodents and man causing in the latter diseases of the group under discussion.

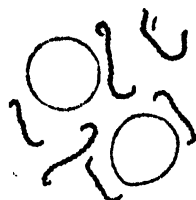


Figure 65 :
Leptospira.

WEIL'S DISEASE, OR INFECTIVE JAUNDICE

Definition.—Weil's disease is an acute infectious disease of sudden onset, characterized by fever, jaundice, albuminuria, hæmorrhages from mucous surfaces, extreme prostration, muscular pain and tenderness, and occasionally a petechial rash; it is caused by a spirochætal organism of the genus *Leptospira*, which is a common infection of the urinary tract of rodents and which infects man through abrasions in the skin and mucous membranes, or by the oral route.

Historical.—Infective jaundice is not a new disease. Early in the nineteenth century, French writers described the disease and reported small outbreaks of it in Europe. In 1886, Weil gave a clear description of the disease and from that time onwards it began to attract considerable attention. At this stage of its history, the disease was a clinical and histopathological syndrome only, and probably more than one causal organism was involved in the epidemics described. However, in 1915–16, when Inada in Japan and Uhlenhuth in Germany associated leptospiral infections with this syndrome, there was a considerable revival of interest in Weil's disease, and it was soon shown to have a widespread distribution.

EPIDEMIOLOGY

Geographical distribution.—It occurs in Japan, Holland, Great Britain, France, Germany, Sweden, U.S.A., Africa, and India and neighbouring countries. In Japan, about 1,000 cases are reported annually, in Great Britain about 100 cases, in Holland a larger number and in other European countries a varying number, probably more or less in proportion to the amount of attention that is paid to the disease. During the 1914–18 war, the disease was common among the troops serving on the Western front. So far as India and her immediate neighbours are concerned, a small number of cases have been reported from time to time by different workers from several places such as the Andamans (Barker, 1926), Rangoon, Calcutta, Bombay, Madras, and the North-West Frontier Province. In most of these places the disease occurs in a sporadic form. For example, in Calcutta within the last seven years some 50 or more cases have been reported. In the Andamans, a sharp outbreak occurred in 1929 in which less than a hundred cases were recorded, but now that its presence has been recognized a large number of cases have been diagnosed each year.

Epidemic status.—On account of the very low incidence, the disease is not at present one of very great public health importance in any tropical

country, with the possible exception of the Andaman Islands, but there are indications that it may be much more widespread than it appears to be at present.

In temperate countries its occupational character stands out so clearly that it comes within the purview of workmen's compensation acts. It occurs in those who come in contact with water or slime contaminated with the urine of infected rats. Sewer and canal workers, miners, fish-handlers and butchers, agricultural labourers, sugar-cane cutters, bargemen and soldiers fighting in trenches are liable to suffer from it.

In the Andamans, the disease is found chiefly amongst agricultural labourers many of whom are adult males who have to work standing in water during part of the year. However, in Calcutta, Das Gupta, who has confirmed the diagnosis in 40 to 50 cases during the last few years, found no association with any particular occupation. Moist soil, moderate temperature, insanitary conditions, and rat infestation favour incidence. In cities, sporadic cases may occur amongst the general population. The larger outbreaks are generally confined to swampy areas, to mines and to canal and coastal regions, but even in the largest outbreak the number of cases is never more than a few hundred.

Seasonal incidence.—In cooler countries, it is a summer and autumn infection, but in the tropics the disease occurs most frequently during or after the rains, and with the onset of dry cold weather it tends to disappear.

Race, sex, and age incidence.—It occurs in people of all races, and in both sexes, but few cases have been reported amongst children. The majority of the occupational groups have consisted of men only, but, in the case of the fish-handlers, they were mostly women.

ETIOLOGY

The causal organism.—*Leptospira icterohæmorrhagiae* is a spiral organism, 6 to 9 μ long and 0.25 μ thick. It has a large number of closely wound spirals, which give it a rope-like appearance; the ends are usually hooked. It is actively motile, and is best examined with dark-ground illumination. It grows well on serum media, such as Noguchi's, Fletcher's, or Vervoort's medium, but takes a week to grow.

Serological strains.—There are a large number of serological strains of leptospira known. Of these at least three strains have been recovered from the cases occurring in India. Whilst there is a tendency towards a geographical grouping of these strains, in the same outbreak more than one strain may be isolated.

Resistance.—*Leptospira icterohæmorrhagiae* is a comparatively hardy organism and remains alive in moist earth, water or food for about three to seven days. Heat and antiseptics readily destroy these leptospiræ; they are killed in half an hour at 55°C. They are also very susceptible to acids and are rapidly killed by hydrochloric or sulphuric acid in dilutions of 1 in 30,000. Mercury perchloride solution in a dilution of 1 in 2,000 kills them in ten minutes.

Distribution in the body and excreta.—It is a blood infection during the first week of the disease, and during this period leptospiræ will be found in most of the internal organs, especially the liver, spleen and kidney. Later, the leptospiræ disappear from the blood, and the kidney becomes

the main focus of infection; from the kidney foci they escape with the urine and may be excreted by this route for a month or more.

Source and mode of spread of infection.—Rats are the chief source of infection. Leptospirosis is primarily a disease of rats, and from rats the infection is transferred to man. Mice also may act as a source of infection. Up to 40 per cent, or even more, of wild rats have been found infected in nature in the countries where the disease is common. In Calcutta, however, Knowles and Das Gupta found the infection rate in rats to be very low, less than 1 per cent, but later Das Gupta found a higher incidence in rats from the dock area, and, in Bombay, Lahiri (1943) found 12 per cent of the rats infected. Taylor and Goyle (1931) obtained similar results in the Andamans. Lewis (1942) found 11 per cent of rats infected in Philadelphia. In the United States, as the blood of dogs has been found to agglutinate leptospiræ in high titre (Packchianian, 1941) and others have been found infected, they are suspected as reservoirs.

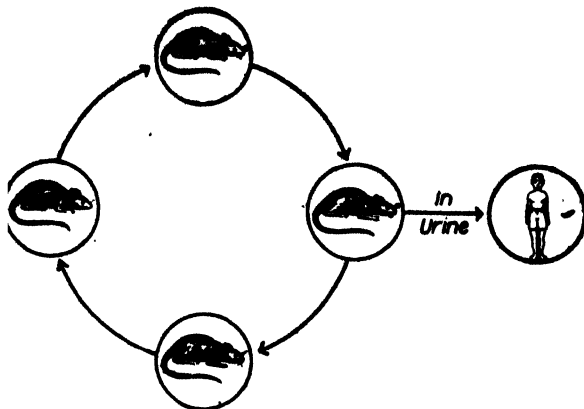


Figure 66 : The transmission cycle in Weil's disease.

Infection in the rat.—In the rat the organisms are present in the blood in the early stages of the infection, but do not cause severe disease or death. Later, the infection becomes localized in the kidney, and from there the organisms are excreted in the urine intermittently, for a considerable period, and sometimes throughout the rat's life. The infection may possibly be transmitted from rat to rat directly through a bite; organisms are found in the mouths of infected rats, and, if these infected rats bite healthy ones, infection will be transmitted, but it is probable that, in most cases, rats become infected by the same routes as man, namely by contact with, or ingestion of, infected material.

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There is no evidence that any insect is concerned in the transmission of infection in these animals.

The urine of infected rats contaminates soil, water and food. Pathogenic leptospiræ have been recovered from such infected waters. As we have noted above, in soil, water, etc., the organisms are capable of living for about three to seven days, but in favourable conditions, e.g. in the slime at the bottom of canals, slowly-moving rivers, docks, etc., they can probably live saprophytically for a considerable time; from these sources man gets infected.

A patient may pass viable organisms in his urine for one or two months, and thus also act as a source of infection; in many of the Andamans cases, organisms were found in the urine from the ninth day of illness onwards to as late as the forty-fourth day, viable leptospiræ being discharged in the urine intermittently, but this is probably not an important method of the spread of infection.

As pathogenic organisms have so frequently been found in contaminated waters, it is suggested that the rat may not be an important link, but that it may simply be a disseminator of infection. Another suggestion is that passage through the rat determines the pathogenicity of the organism. The

balance of evidence is, however, in favour of the rat's playing some essential part in the transmission of the disease to man.

Route of entry.—The organisms enter either by the mouth or through the skin. The latter is considered to be the more frequent route of entry. Organisms generally enter through abrasions in the skin, though they are capable of penetrating even the unbroken skin and mucous membrane. Prolonged contact with infected water and soil facilitates entry. Bathing and accidental immersion in infected water have frequently given rise to the disease, and in Holland a large percentage of the sufferers are thus infected. In most of the Calcutta cases, the route of entry was probably the mouth.

Immunity.—From the sporadic nature of the incidence of the disease, even in the presence of a heavy source of infection, it would appear that man enjoys some natural immunity against leptospira infection. After recovery from an attack of the disease, a high degree of immunity develops. This acquired immunity is mainly due to the presence of specific antibodies. Convalescent serum has therefore been used in treatment (*vide infra*), as well as the serum of immunized horses, which in some countries has been used extensively.

Active immunity can be produced by means of a specific vaccine.

Das Gupta (1942) confirmed the observation that inoculation in man produces a serum that is protective to guinea-pigs, but found that this immunity lasts for less than a year.

PATHOLOGY

The leptospiræ will be found in most organs in the body, but particularly in the liver, kidney and spleen; it is in these organs that most of the pathological changes occur.

Morbid anatomy.—The liver is enlarged and usually yellow; there is degeneration of the parenchyma cells, which will vary from degeneration of isolated cells, to similar changes in localized areas, and to complete disorganization of the whole liver structure, similar to, but usually not so extensive as, the changes that occur in yellow fever. Where isolated parenchyma cells are affected, they die, but are replaced, so that, unless the damage is very extensive, complete recovery is possible.

In the kidneys, there is invasion of the inter-tubular tissues where small hæmorrhages occur, and degenerative changes occur in the tubular epithelium; regeneration follows in the latter case, but the interstitial changes will sometimes, though rarely, lead to a chronic nephritis.

The spleen is slightly enlarged but is soft and diffuent, so that attention is not usually drawn to it clinically; there is hyperplasia of the lymphatic tissue.

Similarly, there is hyperplasia of the lymph nodes in other parts of the body, particularly of the abdominal glands. The bone marrow shows leucoblastic hyperplasia with erythroblastic depression. There may be petechial hæmorrhages in the mucous membrane of the stomach and intestines, or even extensive hæmorrhages into these organs.

Blood picture.—There is usually a leucocytosis of 10,000 per c.mm., a polymorphonuclear percentage of 80 to 85 with a leftward shift in the Arneeth count, and a progressive anæmia; the indirect van den Bergh reaction

is usually positive even in an-icteric cases, and in the cases with jaundice it is biphasic and may reach 60 units of bilirubin.

Urine.—There is usually a heavy cloud of albumin and often traces of blood; occasionally, hæmaturia may reach macroscopic proportions. There is sometimes a decrease in the urea excretion, and later, after a period of anuria, there will often be a temporary increase. Later, in the jaundiced cases, bile will appear.

SYMPTOMATOLOGY

The attacks vary very considerably in intensity, and from serological evidence it is clear that the infection may be sub-clinical. More than half the clinical cases show no jaundice and febrile attacks are relatively mild. In its severest form the disease is difficult to distinguish from yellow fever, as was demonstrated in the classical instance when Noguchi discovered the leptospira in patients who had been shown to him as cases of yellow fever, and for a brief space of time, until the mistake was discovered, *Leptospira icteroides* was proclaimed as the causal organism of yellow fever.

The incubation period is from four to twelve days and the onset is usually sudden. The fever mounts rapidly to reach 102°F. or 103°F. on the fourth day, continuing as a high remittent fever for a few days and then falling by lysis, the whole attack lasting about 10 days. A febrile relapse after about three or four days of freedom from fever is not uncommon. In severe and complicated cases the fever may last much longer, and tends to occur in a series of relapses.

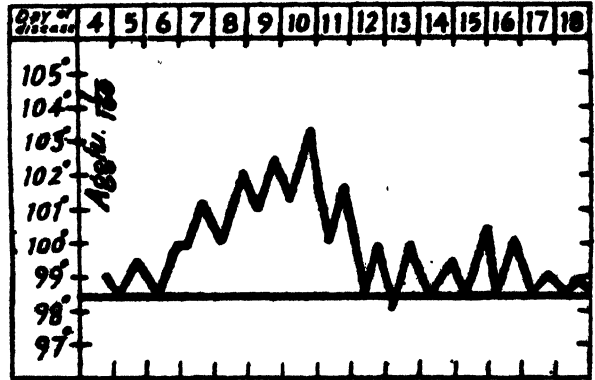


Figure 67 : Temperature chart in Weil's disease.

The pulse is rapid at first but often slows down when the jaundice appears. Other symptoms are headache, stiffness of the neck, photophobia, marked redness and injection of the conjunctivæ, pains in the muscles and joints, vomiting, and severe prostration. Jaundice appears on the fourth day or later, but it is by no means a constant symptom, actually occurring in less than half the clinical cases. The tongue is thickly coated, and there is usually obstinate constipation, though onset with diarrhœa is reported. Epistaxis and bleeding from the gums are common, and hæmorrhages from other mucous surfaces may occur. Rashes are not constant; a petechial rash may appear from the third to the fifth day, and a morbilliform rash from the fifth to the twelfth day : in very severe cases the rash is hæmorrhagic.

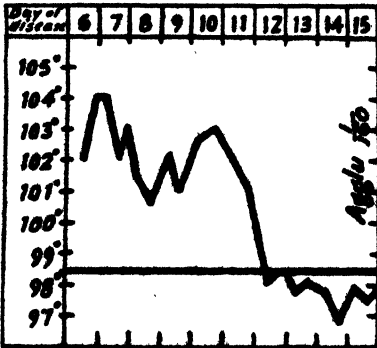


Figure 68 : Case showing an early fall of temperature.

Anuria is not uncommon, and, even when some urine is being excreted, there is evidence of nitrogen retention.

The hair tends to fall out, and, in milder forms of this infection, this is sometimes the first observation of the patient.

The liver is usually palpable and the spleen occasionally so; the former is nearly always tender.

Complications.—The most important complications are bronchitis and broncho-pneumonia; this is particularly true in cold countries.

Iritis and irido-cyclitis have been described in some countries.

Relapses.—In about 30 per cent of febrile cases, there is a relapse of the fever at the end of the third, or early in the fourth, week. This recurrence of fever is not accompanied by any reappearance of the leptospiræ in the blood, and is therefore not a true relapse, comparable with that which occurs in certain other spirochætal diseases. In this second bout, the fever does not usually rise much above 100°F.; the temperature is usually irregular for a few days, and then falls again to normal.

DIAGNOSIS

The diagnosis of Weil's disease, with any degree of certainty, on clinical grounds alone, is not easy, especially in cases in which there is no jaundice. Demonstration of the causal organism in the blood or urine is the surest method of confirming the diagnosis, but strong presumptive evidence may be obtained from the agglutination test.

Leptospiræ are present in the blood of patients during the first week of illness, and can be isolated readily even as late as the ninth day. Microscopic examination of the blood either by means of stained films or by dark-ground illumination is of little practical use, as the leptospiræ are scanty and therefore very difficult to find by this means.

Cultural examination gives fairly satisfactory results. Vervoot's medium is the best to use; into 10 c.cm. of Vervoot's medium, 1 c.cm. of blood is inoculated and the medium is incubated for at least one week, either at room temperature or at 28° to 30°C. In 60 to 80 per cent of cases examined within the first week, positive results are obtained.

Animal inoculation is perhaps the most reliable method of diagnosis. Three to five cubic centimetres of blood are injected intra-peritoneally into young guinea-pigs weighing about 250 grammes, and their peritoneal fluid examined for leptospiræ by dark-ground illumination from the seventh day onwards. If the animal dies, a post-mortem examination is done, and sections of the liver and kidney are stained by Levaditi's method and examined for leptospiræ.

The urine of patients may also show leptospiræ; they appear in the urine from about the tenth day of the illness, and may continue to be excreted for two months. Repeated examinations are however necessary to detect the organisms in the urine, as they are passed intermittently, and usually only a few are present. The urine examination should be done by dark-ground illumination, by culture, or by guinea-pig inoculation. For these, it is best to use the sediment obtained by centrifugalization of the urine.

Serological methods for the diagnosis of Weil's disease have also been developed. The patient's serum and a weak formalinized culture of

leptospiræ are used; agglutinins begin to appear in the blood about the sixth day of illness, and are present for years after recovery. Positive results in dilutions as high as 1 in 10,000 are common, and occasionally the titre rises to 1 in 1,000,000, but an agglutination of 1 in 100 is considered specific by some workers. Such a low titre might indicate past infection, and, as in the Widal test, more attention should be paid to a rising titre. As there are several serological strains of leptospiræ, the serum should be put up with all the strains that are available. In some cases the urine also gives a positive agglutination test up to 1 in 250 dilution.

Recently, Brown (1939) has described an **adhesion test** for the diagnosis of Weil's disease. The patient's serum is mixed with a young culture of leptospiræ, a living culture of some motile bacillus, and fresh serum from a guinea-pig; the mixture is incubated at 37°C. for half an hour. It is then examined under dark-ground illumination. A positive result is indicated by the motile bacilli adhering to the leptospiræ.

DIFFERENTIAL DIAGNOSIS

In severe cases, the clinical picture will suggest yellow fever; in less severe cases, 'bilious remittent' malarial fever or relapsing fever; in the last two, blood examination will clinch the diagnosis. In cases in which jaundice is prominent, catarrhal jaundice will have to be excluded, but the fever will be lower and the prostration less in the latter case. Severe hæmaturia may simulate the hæmoglobinuria of blackwater fever, but careful investigation will distinguish them. Mild cases may suggest dengue, or sand-fly fever, but the leucopenia which is the rule in these conditions, as well as the shorter duration of the fever, should help to distinguish them.

PREVENTION

Successful control and prevention of Weil's disease depends upon—(a) the destruction of rats, (b) the disinfection of infected water and soil, (c) the protection of persons who are exposed to infection, and, in some circumstances, (d) the diagnosis and treatment of cases and disinfection of their urine.

(a) *The destruction of rats.*—As rats are the main source of infection, war against rats is of the greatest importance. Food stores and supplies should be protected by rat-proofing. Attempts should be made to trap or poison rats and reduce their numbers.

(b) *The disinfection of infected water and soil.*—Contaminated water should not be used for bathing, washing, or drinking. Infected water and soil should be disinfected, the latter by the use of calcium cyanamide; this is a fertilizer and is of special value in damp and water-logged agricultural areas. About 168 lb. of calcium cyanamide are required for one acre of soil. For the disinfection of water in paddy fields, 44 lb. of the fertilizer should be used per acre for each inch of depth of water. Leptospiræ generally thrive in alkaline soils. Acidifying the soil also helps to destroy the organisms. Wherever possible, drainage of the soil should be effected.

(c) *The protection of persons who are exposed to infection.*—People working in water or soils infected with leptospiræ should wear sound boots to prevent infection occurring through the skin. They should be warned regarding the danger of using infected water for bathing, washing, or drinking. Before taking food they should thoroughly wash their hands with clean soap and water. Persons with achlorhydria should be particularly

careful. Cuts and abrasions received by workers should be promptly disinfected.

In population groups under special risk, vaccination should be considered, but, as there are a number of serological strains of leptospira, the local strains should be used in the preparation of the vaccine, in order to obtain the best results; this vaccine should consist of 50 to 75 millions of dead leptospiræ per c.cm., and the two inoculations should be given at an interval of a week. According to Inada, this vaccine has helped considerably to reduce the incidence of the disease in Japan. The protection is however apparently short-lived, and re-vaccination should be carried out at regular intervals of certainly not less than a year.

(d) *The diagnosis and treatment of cases and disinfection of their urine.*—Cases should be diagnosed early and admitted into hospital, if possible. Their urine should be disinfected. Convalescents should be detained until their urine is free from leptospiræ.

Convalescents may be re-employed as labourers about two months after recovery. It is advantageous to employ them as they will be immune to infection.

TREATMENT

The only specific treatment that has been effective is specific anti-serum, either horse serum, which has now been prepared on a commercial scale, or convalescent serum. An initial injection of 60 c.cm. of horse serum in a pint of saline should be given intravenously, with the usual precautions against anaphylactic shock; this should be repeated next day, and each day, as long as it is indicated by the patient's condition. A polyvalent serum, or better still one prepared from all local strains, should be used. Of convalescent serum, about 30 c.cm. is usually given and this is also repeated, if necessary.

Arsphenamine has no specific action in this infection.

A pint of 5 per cent glucose in pyrogen-free water and 5 units of insulin should be given, as long as there is evidence of toxæmia. In less severe cases, isotonic rectal saline with 4 grains of calcium chloride to the pint is useful.

Otherwise, the treatment is symptomatic and must be indicated by the complications that arise. The patient should be confined strictly to bed until some days after the temperature has fallen to normal, and he should be kept on a fluid diet, glucose, albumen water and lime whey at first, then milk, and the diet should be increased very slowly during convalescence.

PROGNOSIS

The mortality from the disease is very variable and ranges from 2 to 50 per cent. Death seldom occurs in the an-icteric cases, but in the writer's experience the death rate even under hospital conditions in cases with well-developed jaundice is as high as 50 per cent.

Age is an important factor; in mild epidemics the deaths are often only amongst persons over 50 years of age. The following is the percentage case mortality recorded in different countries: in Japan 32 to 48 per cent, in Malaya 30 per cent, in India 18 to 40 per cent, in Scotland 25 per cent, in Germany 13 per cent, in London 4 to 6 per cent, in Belgium 4 to 6 per cent and in Italy 2 per cent. These figures are based on clinically diagnosed cases and the higher figures probably exclude the mild an-icteric cases.

SEVEN-DAY FEVER OF JAPAN

Introduction.—This is one of the milder forms of leptospiral infection; the syndrome has been recognized in Japan for many years, and is known by the names *nanukayami* or *sakusku* fever. Autumn fever is probably a variant of the same infection. It was distinguished from dengue and shown to be caused by a leptospira (*Leptospira hebdomadis*) by Ido, Ito and Wani in 1918.

There are many recognized strains of *L. icterohæmorrhagiæ* which differ from one another antigenically but are apparently similar in their pathogenicity; at least, up to the present, little correlation between particular strains and degrees of pathogenicity has been demonstrated. The obviously low pathogenicity of *L. hebdomadis* constitutes a difference which at present seems to warrant special differentiation, but nevertheless, in time, intermediate strains may be encountered, and it may then be necessary to consider *L. hebdomadis* as simply one strain of *L. icterohæmorrhagiæ*; in such circumstances, seven-day fever will have to be looked upon as a mild form of Weil's disease, which from a clinical standpoint it might well be.

Autumn fever, pseudo-dengue, and certain other short fevers of Java and Sumatra will also probably fall into line.

Epidemiology.—It is a sporadic infection, common in certain rural districts of Japan, mainly affecting field workers.

ÆTIOLOGY

The causal organism, *Leptospira hebdomadis*, is morphologically identical with *L. icterohæmorrhagiæ*, but antigenically it is quite distinct. In guinea-pigs, it causes a febrile disease which is sometimes fatal, but it produces jaundice in only about 17 per cent of animals infected; cf. *L. icterohæmorrhagiæ* which is almost always fatal and causes severe jaundice in 100 per cent of animals.

Transmission.—The reservoir of infection is the short-eared field-mouse, *Microtus montebelloi*; the leptospiræ are found infecting the kidney in about 3 per cent of these mice in Japan, and infection is transmitted to man by the same routes as in *L. icterohæmorrhagiæ* infection.

SYMPTOMATOLOGY

The onset of this disease is usually sudden, with high fever, headaches, muscular pains, loss of appetite, glandular enlargement, and occasionally a morbilliform rash. The fever sometimes runs a dengue-like course, and in fact the disease was, and probably still is, confused with dengue. Otherwise, it is like a mild form of Weil's disease.

Little is known of the pathology, as the prognosis is uniformly good.

The diagnosis is made in the same way as that of Weil's disease.

The main points of distinction between this disease and dengue are the slow pulse and the leucopenia in the latter; the white cell count in seven-day fever is usually about 10,000 per c.mm., and the increase is mainly in polymorphonuclears.

The treatment is symptomatic; and the preventive measures that can be adopted are based on the knowledge of the reservoir of infection and common-sense application of this knowledge.

REFERENCES

- BARKER, F. A. (1926) .. Leptospirosis with Special Reference to Existence of *Spirochaetosis icterohæmorrhagica*, or Weil's Disease, in the Andaman Islands. *Indian Med. Gaz.*, **61**, 479.
- BROWN, H. C. (1939) .. A rapid presumptive serological test for Weil's Disease. *B. M. J.*, **2**, 1183.
- DAS GUPTA, B. M. (1938) .. Leptospirosis in India. *Indian Med. Gaz.*, **73**, 449.
- Idem (1942) .. Observations on some Immunological Aspects of *Leptospira icterohæmorrhagiae*. *Indian Med. Gaz.*, **77**, 28.
- Idem (1942a) .. *Spirillum minus* Infection acquired from an Indian Squirrel (*Sciurus sp.*). *Indian Med. Gaz.*, **77**, 541.
- IDO, Y., ITO, H., and WANI, H. (1918). *Spirochaeta hebdomadis*, the Causative Agent of Seven Day Fever (Nanukayami). *J. Exper. Med.*, **23**, 435.
- INADA, R. (1917) .. The Clinical Aspects of *Spirochaetosis icterohæmorrhagica* or Weil's Disease. *J. Exper. Med.*, **26**, 355.
- LEWIS, M. (1942) .. The Incidence of *Leptospira icterohæmorrhagiae* in Trapped Rats in Philadelphia. *Amer. J. Trop. Med.*, **22**, 571.
- NOGUCHI, H. (1918) .. Morphological Characteristics and Nomenclature of *Leptospira (Spirochaeta) icterohæmorrhagiae* (Inada and Ido). *J. Exper. Med.*, **27**, 575.
- PACKCHANIAN, A. (1941) .. Positive Agglutination Tests in suspected Cases of Weil's Disease. *U. S. Pub. Health Rep.*, **56**, 2145.
- TAYLOR, J., and GOYLE, A. N. (1931). Leptospirosis in the Andamans. *Indian Med. Res. Mem.*, No. 20. Thacker, Spink and Co. (1933), Ltd., Calcutta.
- UELENHUTH and FROMME (1916) .. Zur Ätiologie der sog. Weil'schen Krankheit (ansteckende Gelbsucht). *Berliner Klin. Woch.*, **53**, 269. (Abstract—*Trop. Dis. Bull.*, **3**, 54.)
- WALCH-SORGDRAGER, B. (1939) .. Leptospiroses. *Bull. Health Organization, League of Nations*, **3**, 143.
- WEIL, A. (1886) .. Über eine eigentümliche mit Milztumor, Ikterus und Nephritis einhergehende akute Infektionskrankheit. *Deut. Arch. klin. Med.*, **39**, 209.

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THE TYPHUS FEVERS

Definition.—The typhus fevers are a group of febrile diseases of varying severity, caused by micro-organisms of the genus *Rickettsia*, and transmitted to man mainly if not entirely by the agency of insects.

Introduction.—In view of the fact that all the diseases hitherto recognized clinically as typhus have been shown to be rickettsial in origin, and that all diseases that are known to be caused by rickettsiæ have some clinical features in common with the recognized typhus fevers, it seems logical, in our present state of knowledge, to include all rickettsial diseases under the general name typhus, with the full appreciation of the fact that at some, probably not very distant, future date, we may have to modify this nomenclature. Some years ago, Megaw pointed out that there were 27 different names applied to diseases of this group, and urged the necessity for clarification and classification; since he wrote this, the number has been added to. He suggested a simple epidemiological classification, which has formed the basis of most subsequent classifications. From the point of view of the clinician, the important point is to distinguish between the epidemic form and the endemic or sporadic forms.

There are many forms of the disease in many countries, but, as it is not expedient, nor would it be possible in the space at his disposal, to discuss all these, the writer proposes to describe only certain clear-cut types that have appeared in countries outside India and then to discuss the disease as we see it in India.

Historical.—Typhus fever was distinguished from typhoid fever only about a century ago both by Stillé (1838) and Gerhard (1837), though there are many earlier historical references to epidemics that were almost certainly typhus. It

was always recognized as a very infectious disease, but the manner in which it spread from man to man was not known until early in the present century, when Nicolle and Conseil (1911) transmitted the infection to apes by the agency of lice. Meanwhile, Ricketts (1906) had transmitted Rocky Mountain spotted fever to guinea-pigs by the bite of ticks, and later he and Wilder (1911) reported the finding of the organisms, that are now known as *Rickettsia*, in the gut of infected lice in Mexico, but it was not until some years later that the aetiological associations of these diseases with the rickettsiae were placed on a satisfactory basis (Wolbach, 1919; 1923; 1925). In 1916, da Rocha-Lima published the first adequate description of the rickettsiae, and gave the name *Rickettsia prowazeki* to the causal organism of epidemic typhus. Wolbach (1919) recognized organisms of the same group, which he called *Dermacentrozetes rickettsi*, as the cause of Rocky Mountain spotted fever. Japanese river fever, or tsutsugamushi disease, which had long been recognized clinically and known to be transmitted by mites, was shown to be caused by a rickettsia, which Sellards (1923) described and called *R. orientalis*; the mild sporadic form of typhus that Brill (1898) described in New York, the slightly more severe but still mild sporadic form that occurred in Mexico and South-East United States (Maxcy, 1926), and 'trench fever' that occurred on both sides of the western front in the last war, were also shown to be rickettsial in origin; in 1925, the endemic typhus fevers of Malaya were linked up with this group of diseases by Fletcher and Lesslar, and the position was clarified by Lewthwaite and his collaborators (Lewthwaite and Savor, 1940). In 1937, Burnet and Freeman showed that Australian 'Q' fever (Derrick, 1937) was caused by a rickettsia.

Wilson (1909) reported the isolation from the stools of typhus patients of proteus-like organisms that were agglutinated by the patients' sera, and later Weil and Felix (1916) separated the special strain of proteus that gave a very high agglutination titre with the serum of patients suffering from epidemic typhus, thereby introducing the test, now usually known as the Weil-Felix or the Wilson-Weil-Felix test, which appears to be positive in most of the typhus fevers and is a further means of identifying them.

In 1917, Megaw drew attention to the existence of endemic typhus in India, and suggested the tick as a transmitter.

Thus, during the last thirty years, a number of diseases, which occur in many different parts of the world, have little in common epidemiologically, and are clinically often very dissimilar, have been linked up and shown to be caused by some species of the genus *Rickettsia*. It has only been possible here to outline the story and to mention a very few of the workers involved, some of whom, including both Ricketts and von Prowazek, lost their lives during their investigations, as the result of laboratory infections.

Classification.—Since Megaw suggested his classification according to the vector, a considerable advance has been made in our knowledge of the antigenic relations of the various rickettsiae that infect man. On an immunological basis, there are four main groups of typhus fever: (a) classical typhus (with which endemic typhus is closely related), (b) Rocky Mountain spotted fever, (c) tsutsugamushi, and (d) trench fever.

The classification that has been adopted here is modelled on Megaw's original classification, which has been modified to take into account recent work on the antigenic relationships of the rickettsiae, and to indicate the nature of the primary rickettsial transmission cycle. The three main divisions in the classification indicate the *primary* transmission cycles; for example, epidemic, that is from man to man, 'epiarthropodic' (a word introduced provisionally by the writer), that is from arthropod to arthropod, and epizootic, that is (in this instance) from rodent to rodent. This provisional classification is shown in table II, which also gives some of the outstanding clinical and other features of these diseases.

There are still certain typhus fevers which have not found their places in either of these classifications, notably the typhus fevers of Kenya and South Africa, those of India, which we do not look upon as a homogeneous group, and the newly described 'Q' fevers of Australia and America. Further reference is made to these below.

TABLE II: FEVERS OF THE TYPHUS GROUP

Primary cycle	Epidemic	'Epiarthropodic'	Epizootic		
			Sporadic place-diseases communicated from natural reservoirs to man by various arthropoda. Mostly diseases of the open country.		
Vector classification	Epidemic		Epizootic		
	Communicated from man to man. Associated with famine, filth and overcrowding.	Diseases of special circumstances.			
	Louse-typus				
Names and synonyms	Classical type typhus fever; typhus exanthematicus.	Trench fever. Weigl's disease			
Distribution	Cosmopolitan. Less common in the tropics.	War conditions. Laboratory infection.			
Virus	<i>Rickettsia prowazeki</i> .	<i>R. quintana</i>			
Vectors	Human lice (<i>Pediculus humanus</i>).	Human lice			
Reservoirs of infection	Man	Lice			
Serum agglutination response to	+++	?			
	+				
Rash	Macular or papular often faint. Rare on palms, soles and face.	Pink macules or papules.			
Local sore, lymphangitis and lymphadenitis.	Nil	Nil			
Mortality, per cent	5 to 50	Very low			
			Rocky Mountain spotted fever, western variety.	Flea-typus	Mite-typus
			Rocky Mountain States U.S.A.	Europe, South America, Africa, Asia.	Taungamushi, Japanese river fever, scrub or tropical typhus, Sumatra mite-fever.
			<i>R. rickettsi</i>	<i>R. conorii</i>	<i>R. orientalis</i> .
			<i>Dermacentor andersoni</i> .	<i>Rhipicephalus sanguineus</i> .	Mites (<i>Trombicula akamushi</i> and <i>T. deliensis</i>).
			<i>Dermacentor andersoni</i> (no animal reservoir identified).	Rodents of the wilds; possibly dogs and other domestic animals.	Rats and mice.
			+	+	— to ±
			+	+	—
			+	+	++ to +++
			Maculo-papular, common on palms, soles, and face.	As in louse-type but often faint or absent.	Macular or papular. often on face, rare on palms and soles.
			Nil	Common	Almost constant in Japanese mite-typus: often absent in other mite-typuses.
			High, 10 to 80	Low, about 2	10 to 60

CLASSICAL, EPIDEMIC, OR LOUSE-BORNE TYPHUS

Definition.—Classical typhus is a severe febrile epidemic disease with a sudden onset, lasting 10 to 15 days and ending in rapid lysis, accompanied by a rash that appears from the third to the fifth day, and caused by *Rickettsia prowazeki* which is carried from man to man by lice.

EPIDEMIOLOGY

Geographical distribution.—This disease has, or rather has had, a world-wide distribution. It is certainly not 'tropical', though it might be considered *exotique*; it is actually much less common in tropical than in temperate countries.

Recent epidemics have occurred in Russia, Poland, the Balkans, Ireland and Spain in Europe; in North Africa; in Asia Minor, Transcaspia, Siberia and China; and in Columbia, Ecuador, Peru and Chile.

Epidemic features.—It is essentially an epidemic disease, and its incidence is clearly explainable on the basis of its mode of transmission. It occurs in the less civilized countries in Europe where the sense of personal cleanliness of the individual is not highly developed, or where through circumstances his normal habits are interfered with, such as during wars, persecutions, and famines. Its absence from many tropical countries can probably be explained by the small amount of clothing worn, which reduces the harbourage of the transmitting louse, and, in the case of India, on the cleanliness of the personal habits of the majority of the population.

In addition to the transmission factor, the lowering of the resistance of the population by hardships and privations is probably important. In such circumstances, the natural and the acquired immunity is lowered, so that the individual not only becomes infected very easily, but antibody formation is poor and the virus is able to circulate unneutralized in the peripheral blood for a longer period than under more favourable circumstances, and therefore causes a heavier infection of the lice.

Deaths from typhus in England and Wales, which numbered about 4,000 annually in 1870, had fallen below 40 at the beginning of the century to disappear from the returns by 1920. The history of the disease in other sanitarilly-advanced European countries has been similar.

Season, race, and sex incidence.—In its seasonal distribution, typhus is more common in winter than in summer for the obvious reason that people tend to sleep herded together in their huts and wear more clothes in winter.

All races appear to be equally susceptible to the disease but it tends to take a milder form in the races habituated to it (Napier, 1919).

The sexes are equally susceptible; the disease is usually milder in children.

ÆTIOLOGY

The virus.—The causal organism is *Rickettsia prowazeki*, the type species of the genus *Rickettsia*. The rickettsiæ are granule-like bodies, more or less pleomorphic, with a diameter of less than half a micron, staining badly with aniline dyes, but well (purplish) with Giemsa's stain; they show a tendency to bi-polar staining. In their behaviour they fall between the filtrable viruses and the bacteria; they do not grow on ordinary

laboratory media, but can be grown in tissue-culture medium; they are held up by the finer filters, whilst passing through the coarser ones, as do small bacteria.

Rickettsial bodies are found in the cytoplasm of endothelial and the smooth muscle cells of the blood vessel walls of their mammalian hosts, and also in the nuclei of the cells; in the cells of the gut lining of lice and other arthropods, an intra-cellular position characterizes the pathogenic rickettsiæ, and distinguishes them from the non-pathogenic varieties that are also found in certain arthropods. In the blood stream the rickettsia tends to adhere to the red cells and platelets.

Transmission.—The virus circulates in the peripheral blood during the febrile period and defervescence. The louse, *Pediculus humanus*, becomes infected by sucking the blood of its host, which is exclusively man; the rickettsiæ invade the endothelial lining of the gut of the louse; here they multiply, the cells eventually burst into the lumen of the gut, and the rickettsial bodies are passed out with the fæces; the cycle within the louse takes at least three days, usually longer, after which the louse is infective and remains so for the rest of its life. The normal life span of the louse is about 14 days, but survival up to 45 days has been reported; the infection, however, tends to kill them. The rickettsiæ survive in the dried fæces of lice up to 60 days, and the fæces are probably the main source of infection of man and the sole source of infection of the next generation of lice. The extreme infectiousness of typhus depends on the fact that the dried fæces of lice may be blown about in the air of the sick-room or laboratory. Man is infected by scratching the fæces into his skin, by contamination of his mucous membranes, or *via* the respiratory tract. It is doubtful if gastro-intestinal infection takes place, and it is

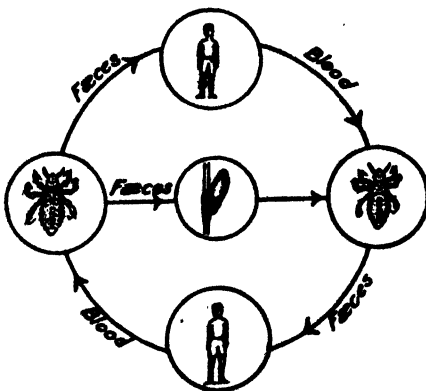


Figure 69 : Transmission cycle in epidemic typhus.

known that infection is not transmitted by the bite of the louse. The cycle is thus man—louse—man. The louse is an essential link and so probably is man, for *Pediculus humanus* feeds exclusively on human blood, and, though the infection may be transmitted to the next generation of lice by contamination, there is no hereditary transmission, and, as the infection is fatal to the louse, no louse-to-louse cycle would survive any length of time.

The possible modes of dissemination of infection are by (a) migration of infected lice, (b) by contact contamination with the infected fæces of lice, and (c) by air-borne infection from dried fæces of lice. The former two have long been recognized, and explain the rapid spreading of the disease when louse-infected people are crowded together, but the possibility of the latter mode was overlooked until recently; it explains the high incidence amongst doctors and nurses, and the many laboratory infections. It was reported in Ireland that during an epidemic, 50 per cent of attending doctors contracted the disease. The same was the experience in Serbia after the last war, when 36 per cent of the doctors in the country died of typhus. Many laboratory infections have occurred, and some of the most prominent workers in this field have died of typhus (*vide supra*).

Immunity.—The immunity produced by an attack is not complete, and second and even third attacks have been reported. The comparatively mild form that the disease sometimes takes in communities where it is common can probably be accounted for by the previous attacks that these people have suffered, especially during childhood when the attacks are often very mild and might not be recognized as typhus.

Passive immunity can be conveyed by the injection of the sera of convalescents, but as a practical means of protection this method is of little or no value.

Active immunity can be produced by the inoculation of dead rickettsiæ (*vide infra*).

Cross immunity between classical typhus and the so-called Brill's disease has been shown to be complete; this is of course natural. A considerable degree of cross immunity between classical and murine typhus (*e.g.* tabardillo of Mexico, *v.i.*) has been demonstrated, though this is not complete, but against the other forms of typhus there is little or no cross immunity. The immunity runs more or less parallel with the Weil-Felix reaction.

PATHOLOGY

Morbid anatomy.—There are few **macroscopic** changes. The spleen is usually distinctly enlarged; on section it is dark red, soft and diffuent. There is cloudy swelling of the liver and kidneys. Waxy degeneration of the muscles has been noted. There are petechial hæmorrhages in the serous and mucous membranes, and in the pons and medulla, and occasionally more extensive hæmorrhages into the hollow viscera, the serous cavities, and even into the ventricles.

Microscopically, the characteristic lesion is produced by endothelial proliferation in the arterioles, a specific reaction to invasion by rickettsiæ, which leads to thrombosis and eventually necrosis; there is a peri-vascular infiltration, first of mononuclears and plasma cells and later of polymorphonuclears. The tubercular nodules that are thus produced in the organs and tissues are suggestive of miliary tuberculosis. These changes take place in the skin and cause the characteristic rash, in the mucous and serous membranes and cause hæmorrhages in the various organs, and in the central nervous system, the neuroglia cells taking part in the reaction, and cause the mental symptoms.

There are no very characteristic changes in the **blood picture**. In severe cases, especially when the patients first come under observation and are suffering some dehydration, there will be polycythæmia; there is usually a leucocytosis of 12,000 to 15,000 per c.mm. and an absence of eosinophils.

The **urine** shows the characteristics that are usually associated with high fever, and often some albumin, but there are seldom casts or other evidence of nephritis.

SYMPTOMATOLOGY

The **incubation period** is usually from 10 to 14 days; extreme instances of incubation periods of 4 and 24 days have been reported.

After a day or two of prodromal symptoms, general malaise, loss of appetite, headache, and joint pains, the **onset** is sudden with the fever rising to its peak, 104°F. or higher, in 48 hours, occasionally with a rigor. This is accompanied by pains in the loins and joints, severe headache,

photophobia, and rigidity of the neck. The face is flushed and bloated, the conjunctivæ injected, the tongue has a dirty brown centre and bright pink edges, the mucous membranes generally are a deep red, the breath is offensive, and there is often epistaxis. There are fine tremors of the extended fingers and fibrillary twitchings of the face, and the speech is hesitant, slow and slurred. Vomiting is common and constipation is a constant symptom. The pulse is full and soft, usually about 100 per minute, and the blood pressure is low.

Nervous symptoms develop early; the patient is drowsy and apathetic, and, during consciousness, cerebation is slow, as early as the fourth day (*cf.* typhoid, in which the mental symptoms develop much later). Then later he becomes anxious and restless, and eventually may become delirious or pass into a stuporous state preceding death in coma.

The temperature, as noted above, rises rapidly to 104°F. and remains as a high remittent temperature for 10 to 12 days; at the end of this period, it may show deep remissions and eventually it falls by rapid lysis. The whole febrile period lasts from 12 to 17 days.

The rash appears on the fifth or sixth day, rarely as early as the third or fourth. It is a profuse roseolar rash on the trunk, limbs and sometimes the face, but not on the palms of the hands or soles of the feet. The macules are comparatively large, varying in diameter from 2 to 7 millimetres, and on the background between the spots there is a general erythema. Ligature of the limb causes an intensification of the rash, and on dark skins it is often only by this device that one can see it. The spots continue to develop for a few days, and they may become petechial or even hæmorrhagic, particularly at the bends of the knee and elbow, and on the feet and ankles. There may be slight desquamation at the fall of the temperature, and there is usually a slight brown stain of the skin, that remains for some time.

Variations from the normal.—The disease described by Brill in 1898 and shown by Anderson and Goldberger in 1912 to be a form of typhus has

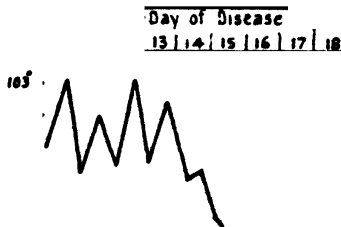


Figure 71: Temperature chart in a case of mild classical typhus which was diagnosed as broncho-pneumonia, but later shown by the Weil-Felix reaction to be typhus (original).

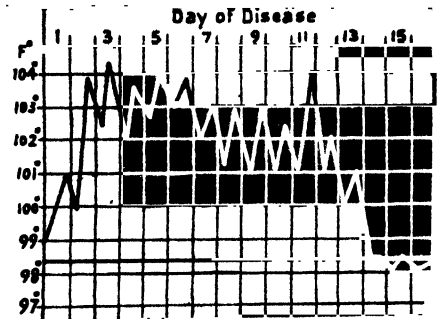


Figure 70: Temperature chart in a case of classical typhus (original).

more recently been shown by Zinsser to be almost certainly a manifestation of late relapse of classical typhus, for he found that in nearly every one of the 538 cases of this disease reported between 1910 and 1933 in New York, the patients were emigrés from Russia or other European countries where typhus is frequently epidemic. This is a clinically mild type of typhus with no mortality, usually with a modified rash which may be absent, but the serum gives the typical agglutination against proteus X19.

Another modified form of the disease in which the clinical picture is typical, except for its benignity, is sometimes encountered amongst populations in which epidemics are common. Such an epidemic occurred amongst Armenian refugees in Mesopotamia in 1918; in this instance the disease was mild amongst the refugees, who were well fed and comfortably accommodated, but was much more severe amongst the Indian and British personnel who were looking after them (Napier, 1919).

Complications.—Broncho-pneumonia is common; other complications are stomatitis, parotitis, and even noma; thrombosis followed by gangrene of the feet or toes, genitals, and ears characterize some epidemics. Heart failure, preceded by a very low blood pressure and a slow pulse, is not an uncommon mode of death.

DIAGNOSIS

In a typical case, the clinical diagnosis will present little difficulty; the points which differentiate typhus from typhoid are: (i) sudden and rapid onset with the early development of severe symptoms, (ii) pains in the joints, limbs, and loins, and rigidity, (iii) the rash, (iv) the nervous symptoms and especially their earlier development, (v) the leucocytosis, and (vi) the earlier and more rapid resolution.

Of the laboratory methods, the **Weil-Felix reaction** is the most valuable. This test is dependent on the probably accidental similarity of the antigenic structure of the specific rickettsia of typhus to that of a bacillus of the proteus group, X19, that was originally isolated from the urine of a typhus patient and found to be agglutinated in a high titre by his serum. Though really a non-specific test, this test is as specific as any 'specific' agglutination test in

non use. At the end of the first , the patient's serum gives a positive result in a dilution of 1 in 100, and by the end of febrile period it may be as high as 1 in 5,000; agglutination persists for some weeks and probably for some years in a low titre, which may be raised by some other febrile attack. It is not safe to accept any agglutination of less than 1 in 125 as suggesting typhus, and moreover a rising titre should be expected, as in the writer's experience a titre of at least 1 in 640 is always reached at some stage of the disease.

More recently, an agglutination test with an emulsion of rickettsiae has been developed, but this test presents no advantages in this form of typhus.

Of the more elaborate laboratory procedures, guinea-pig inoculation is the most useful; about 2 c.cm. of the patient's blood during the febrile period is inoculated into the peritoneum of a young guinea-pig; the guinea-pig will develop the characteristic fever in about eight days, but without scrotal swelling which is the characteristic of other rickettsial infections. Occasionally in the first passage the virus is fixed in the brain and there is no febrile reaction; in such cases the inoculation of an emulsion of the brain of the first guinea-pig into a second will usually lead to the characteristic fever.

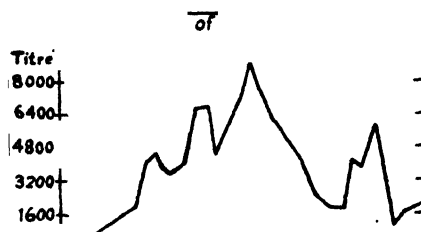


Figure 72: Graph based on the Weil-Felix reactions on 85 samples of serum from definite cases of typhus, taken at different periods during the disease (original).

PREVENTION

In the face of an epidemic the first duty of the doctor is to protect his medical personnel, and incidentally himself. The danger comes from louse infestation, contamination from squashed lice and lice-fæces, and from inhalation of dried lice-fæces. A measure of special importance in this disease is the protection of medical personnel with masks; those dealing with dirty *dry* clothes should wear gas masks. For other details of anti-louse measures, see above (p. 231).

A great deal of attention has been paid to the subject of **prophylactic inoculation** during the last quarter of a century even when the prospects of producing a vaccine for wholesale inoculation seemed very remote, on account of the obvious desirability of protecting medical personnel and laboratory workers. Weigl (1924) produced the first successful vaccine from trituration of the intestines of infected lice; this method had very obviously a limited application. The two methods that now promise success are those of Zinsser and his co-workers (1937) who have produced vaccine on a large scale by the combined agar-tissue-culture and a yolk-sac-culture methods, and of Durand and Sparrow (1940) who have produced a vaccine by inducing massive lung infections in mice by insufflation of rickettsiæ. In animal experiments and for the protection of individual workers subjected to special risk, they have been successful, but, at the time of writing, neither of these methods has been put to the practical test of the protection of large populations during epidemics; however it is probable that ample opportunities will soon arise in Europe if not elsewhere.

We have certainly reached a stage where medical personnel might well be protected in this way, but at present, in most circumstances, the protection of a whole population by this means would be too expensive.

TREATMENT

The treatment is almost entirely symptomatic. Convalescent serum has been used but has not yet established any reputation. The production of antiserum on a large scale has not yet been undertaken, but this may be possible now that the difficulty of getting rickettsial vaccine has been largely overcome.

The patient must of course be kept strictly in bed throughout the fever and for some days after defervescence, and given a balanced diet, mainly fluid, with plenty of additional fluid to drink; the course of the disease is comparatively short, and it is not therefore so necessary to maintain a high calorie diet, as in the case of typhoid, but in milder cases it is advantageous to do so. Hydrotherapy should be adopted to keep the temperature down, and strict attention should be paid to mouth hygiene, and to the skin, particularly pressure points, which should be rubbed well with alcohol. The bowels should be moved by a mild laxative given nightly and, if necessary, by an enema given every second day.

In very dehydrated and toxic cases, intravenous saline has been used with success; in toxic cases, intravenous glucose (5 per cent) is also useful.

A sedative will often be necessary; phenobarbitone should be tried first and then codeine, but, if neither is successful, it may be necessary to resort to morphia. A lumbar puncture will sometimes relieve extreme restlessness. Frequent small doses of brandy are very useful, and cardiac

stimulants may be necessary; camphor in ether or cardiazol is preferable to strychnine or digitalis. Oxygen will often be useful.

PROGNOSIS

The death rate is very variable and will depend on the conditions; for example, in time of famine and amongst half-starved and exhausted refugees, it may be nearly 100 per cent; it will also vary from epidemic to epidemic, but is seldom less than 10 per cent; in children the rate is low and in the aged high. Death usually occurs about the 10th to 12th day.

TRENCH FEVER

Definition.—Trench fever is a febrile disease of moderate severity which shows a tendency to relapse; it is caused by a rickettsial organism, *R. quintana*, which is transmitted to man sporadically from the louse in which it is a saprophytic infection. The disease appeared during the last war, mainly in the trenches on the western front, but also in Poland, Northern Italy and Macedonia, and has subsequently disappeared.

Ætiology.—The causal organism, *Rickettsia quintana*, is apparently a natural parasite of the louse, *Pediculus humanus*, and only infects man sporadically. This rickettsia lives in the lumen of the gut of lice, and is never intra-cellular; its normal cycle is from louse to louse by contamination, and only when he is subjected to intensive dosage with the virus does man become infected. The infection is transmitted from the crushed bodies of lice, or from their fæces, through an abrasion in the skin or *via* the conjunctiva. Man is said to be infective to the louse from the third day of the disease, and to remain so well into convalescence, but the early experimenters who demonstrated this do not seem to have taken the extreme precautions to ensure the cleanliness of their louse stock which recent investigations have shown to be necessary. In fact, all work done on this disease in the past should be repeated and confirmed. There is at present a school of thought which entertains grave doubts as to whether trench fever was caused by rickettsiæ.

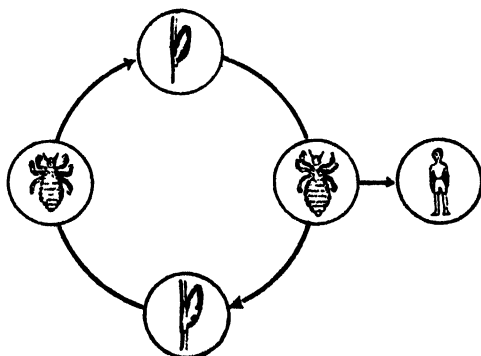


Figure 73 : Suggested transmission cycle in trench fever.

The relation between *R. quintana* (and *R. weigli*, *vide infra*) and *R. pediculi*, the natural rickettsia of the louse, is not clear. These two rickettsiæ are indistinguishable, both morphologically and in their relation to the louse, as they are both extra-cellular and non-pathogenic in the louse, but the latter is normally non-pathogenic to man. It seems possible that, in certain circumstances not yet determined, *R. pediculi* becomes pathogenic to man. As this disease has now disappeared, quite possibly only temporarily, it is impossible to study it, and the rickettsial organism that causes it, by modern methods.

Weigl's disease, which is the name given to a localized laboratory outbreak of rickettsial infection, is almost certainly exactly the same disease; laboratory workers were infected through handling infected lice.

Symptomatology.—The incubation period is eight to ten days. The onset is sudden, usually without prodromal symptoms, but occasionally

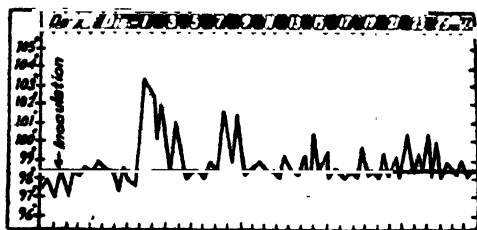


Figure 74 : Temperature chart in trench fever (after Byam, 1923).

there is headache, weakness, restlessness and diarrhoea. In a few cases the onset is so sudden that the patient falls down, or becomes so giddy that he cannot walk; other symptoms are generalized pains, vomiting and gastro-intestinal symptoms. The temperature rises to 103°F., or so, and the fever continues for about three days; it then falls to normal for a day or two, and again rises. The periodicity

varies between four and eight days. There is usually conjunctival injection, a very dirty tongue, occasionally rose spots on the chest, that disappear on pressure, and a slightly enlarged hard spleen. The blood shows a moderate leucocytosis. The diagnosis is largely clinical and circumstantial, and by a process of exclusion. At the present day, it would be unwise to make this diagnosis in the absence of a heavy infestation with rickettsia-infected lice.

Prevention and treatment.—The louse is the essential factor and vigorous measures, indicated above, should be directed against this parasite. Treatment is symptomatic.

ENDEMIC, OR MURINE, TYPHUS

Definition.—Endemic typhus is a fever of the typhus group, of moderate severity, caused by *Rickettsia muricola* (mooseri) which is closely related to, if not identical with, *Rickettsia prowazeki*, and is transmitted to man by the rat flea, *Xenopsylla cheopis*; it occurs endemically in many tropical and sub-tropical countries.

Synonyms, associated diseases, and geographical distribution.—Included under this heading are *tabardillo*, or endemic typhus of Mexico and the south-eastern states of the U.S.A., ship typhus of Toulon (France), urban or shop typhus of Malaya, Manchurian endemic typhus, and certain other flea-borne typhuses reported from different parts of the world, Syria, Greece, Africa, China and Indo-China.

ÆTIOLOGY

The causal organism is usually known as *Rickettsia muricola*, but is also referred to as *R. mooseri*. It is morphologically identical with *R. prowazeki*, and in its behaviour in its arthropod hosts it is very similar to it; in the flea, it is found in the endothelial cells of the lining of the gut, but it does not kill the insect. The only distinguishing characteristic is that *R. muricola* produces scrotal swellings when inoculated intraperitoneally into guinea-pigs, but some doubt has been thrown on the stability of this differentiation by the observation that *R. prowazeki* will acquire this characteristic if it is transmitted through a series of guinea-pigs.

Transmission.—The epidemiological investigations of Maxcy (1926), the later experimental work of Dyer *et al.* (1931), and the co-ordinating studies of Zinsser and his associates have led to a clearer understanding of this disease. These studies have established the following facts. The

main reservoir of infection is the rat (mice and other rodents also possibly act in this capacity), and the infection is passed from rat to rat by the rat louse *Polyplax spinulosus*. This louse is specific to the rat, and does not infest man. But the infection is also transmitted from rat to rat by the rat flea, *Xenopsylla cheopis*, which does in certain circumstances infest man. The rickettsia does not kill the rat louse, the flea, or the rat, so that transmission to man is sporadic and only occurs when the association between the rat and man is very close. (Compare the transmission of plague by the same rat flea: in this case the rat dies, the infected fleas leave the dead rat to find new hosts, either rats or man, and a rapid dissemination of infection takes place, resulting in an epidemic.)

Further, it has been shown that, from man, the louse can acquire the infection with this virus, so that when epidemiological conditions are favourable, a louse-borne epidemic starts. The relationship of these three cycles is shown diagrammatically below:—

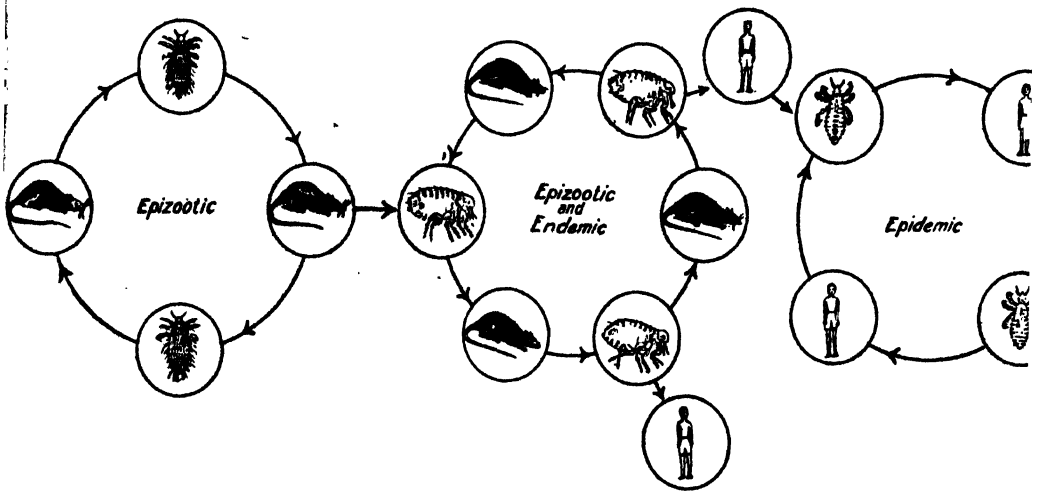


Figure 75.

This demonstrates how the virus of typhus survives during the inter-epidemic periods, and seems to offer a very reasonable explanation for the apparent spontaneous generation of epidemic typhus.

Zinsser has pointed out that the facts of the non-pathogenicity of this rickettsia to the flea, and its lethal effect in the human louse, suggest a much longer association with the former; or in other words that endemic murine typhus was the older disease from which epidemic typhus originated.

Epidemiology.—The disease is endemic and sporadic. It occurs under conditions where man lives in close association with rats: in insanitary prisons, in crowded and insanitary bazars of Mediterranean and eastern ports, on rat-infested ships, and in grain stores.

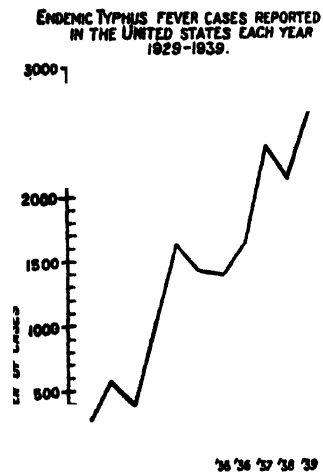


Figure 76 (Dyer, 1941).

In the endemic areas, the incidence of this disease may be such as to constitute an important public health problem, and even in the United States, the annual incidence is in the neighbourhood of 3,000, with a death rate of about 5 per cent.

In most of the endemic areas, it has no special seasonal incidence, but, in the colder countries where it occurs, it is a summer or autumn disease. Individuals of all races and ages and both sexes seem to be equally susceptible.

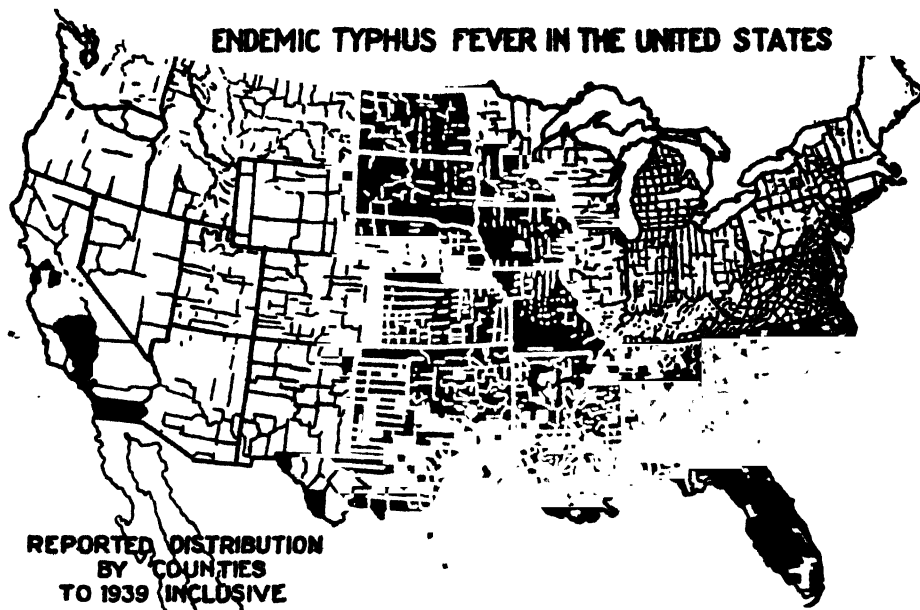


Figure 77 (Dyer, 1941).

The relation of this disease to epidemic typhus has been suggested above. When once the louse-man cycle has been established, the disease takes on all the characters of classical typhus.

Pathology.—This does not differ materially from that of classical typhus, but it has not been studied very thoroughly as deaths are comparatively rare.

Symptomatology.—The disease differs from classical typhus mainly in its intensity. The incubation period is from 10 to 16 days; the onset is sudden and may be quite severe, but the severity is short-lived and the temperature drops to the 100°F. line or so within a few days; the whole course is not usually more than 10 to 14 days. The rash appears about the fifth day, but is less intense. The deaths are usually due to complications, e.g. broncho-pneumonia, but occasionally an isolated case runs a severe course which may be indistinguishable from the classical disease on clinical grounds.

The diagnosis is confirmed by a positive Weil-Felix reaction with the OX19 antigen (*vide infra*).

Immunity.—It is on the immunological experiments that our knowledge of the close relationship of the murine and classical typhus depends. In animals, previous infection with either virus produces a solid immunity against infection with the other; this lasts in some cases up to a year.

Whilst agglutination experiments confirm the existence of this cross-immunity, quantitative experiments show that agglutination will occur in higher dilutions with the homologous rickettsia. Both rickettsial infections lead to the formation of agglutinins against proteus OX19 in animals and man.

There is no cross-immunity against the other species of rickettsia.

Prevention and treatment.—It must be obvious that the preventive measures in this disease are on entirely different lines from those in epidemic typhus. The main attack is on the rat, but it is obviously essential that the rat's fleas must also be destroyed, or they will migrate to other rats and possibly man, and will tend to disseminate the infection. The methods to be adopted are numerous and varied, and will depend very largely on the circumstances (*vide* PLAGUE).

One could not advocate extensive and expensive measures for the sake of limiting this disease alone, but rats carry so many other diseases and cause so much economic loss through their rapacious and destructive habits that any successful measures against these vermin must be a sound investment.

The dangers of heavy louse-infestation in areas of endemic typhus are worth stressing again here, for, even if other circumstances are necessary for the change over to the epidemic form to take place, louse-infestation is a *sine qua non*.

Personal prophylaxis can be effected by inoculation with either the murine or the classical strain.

Treatment is symptomatic, on the lines indicated above.

ROCKY MOUNTAIN SPOTTED FEVER

Definition.—Rocky Mountain spotted fever is a fever of the typhus group, usually of considerable severity and with a high mortality, characterized by an intense maculo-papular rash, caused by *Rickettsia rickettsi* and transmitted to man sporadically by the ticks, *Dermacentor andersoni* and *variabilis*; the disease is endemic in most of the states in the U.S.A., but the Rocky Mountain states are the most heavily infected.

Geographical distribution.—As the name suggests, the disease was first recognized and is most prevalent in the mountain states of the U.S.A., Montana, Idaho, Wyoming, Colorado, Utah and Nevada, also in the Pacific states, especially Oregon. In the last ten years, either the infection has spread towards the eastern states, or more probably the disease has been recognized in these states; the highest incidence is in Maryland, Virginia, and North Carolina, but a few cases have been reported from almost every state in the Union.

The typhus of São Paulo and Minas Geraes in Brazil, and the fièvre boutonneuse of the south of France and the north African coast are closely allied diseases (*vide infra*).

ÆTIOLOGY

The virus.—The causal organism was originally named *Derma-centrozenus rickettsi*, but was later shown to be a rickettsia and re-named *Rickettsia rickettsi*. It has the morphological and tissue-cultural characters of the other intra-cellular rickettsiæ, but is distinguished by its intra-nuclear position. It occurs in nature in the wood tick and in other

ticks. Many wild rodents as well as laboratory animals can be infected, and in the guinea-pig it produces fever and the characteristic scrotal lesion (Neill-Mooser reaction).

Transmission.—The two principal transmitters are the wood tick, *Dermacentor andersoni* (*venustus*), and the dog tick, *Dermacentor variabilis*; the former is the main transmitter in the mountain states and

the latter in the eastern states. In Brazil, *Amblyomma cajennense* is the tick incriminated, and in France the dog tick, *Rhipicephalus sanguineus*.

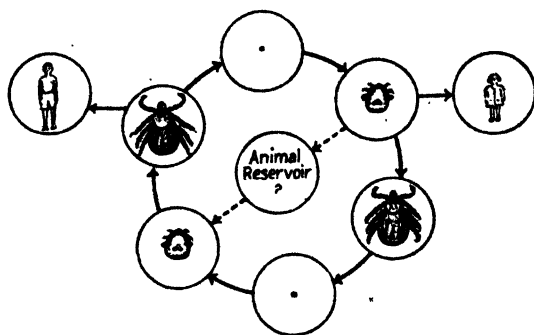


Figure 78: Transmission cycle in Rocky Mountain spotted fever (Western variety).

infection and it seems probable that they help to maintain this widespread sporadic infection. It has however been pointed out that no reservoir is necessary, since the infection is transmitted to the progeny of the ticks, in the case of the main vector *Dermacentor andersoni*, through an infinite number of generations.

The adult ticks bite man and transmit the disease to him, and the nymphs and larvæ will sometimes be found on children. The percentage of ticks infected is comparatively small; in the endemic areas this varies from place to place, and from year to year in the same place, but the general average is about 2 per cent, and it seldom rises above 10 per cent of a sample of ticks examined.

In a starved tick the infection is dormant and it takes some time before it is reactivated. In a recently-fed tick, the infection may be active, and transmission may take place fairly quickly, but it is usually considered that if a tick is removed within four hours, infection will be avoided; a starved infected tick has been fed on a susceptible animal for as long as three days, without transmitting the infection. The infection is transmitted by the bite of the tick.

Immunity.—The immunity produced by an attack is not complete, and many instances of second attacks have been reported. There is no cross-immunity with other forms of typhus, except those that have been recognized as closely allied diseases (*v.s.*). Whilst in both this disease and endemic typhus, the serum agglutinates proteus OX19 and OX2, the rickettsial strains can be differentiated by inoculation into rabbits; in these animals, the Rocky Mountain spotted fever strain will give rise to agglutinins against OX2, whereas the endemic typhus strain will not. Some immunity can be produced by inoculation with a vaccine (*vide infra*).

Epidemiology.—The incidence is sporadic. In the mountain states, it is to some extent an occupational infection, in that those engaged in hunting and trapping game and rodents, and in agricultural pursuits, are most

likely to be infected. Others that are frequently infected include prospectors and miners, highway construction workers, and tourists and pionickers. Thus, ~~men~~ are most frequently infected in these areas, but in the eastern states where the dog tick is the carrier, the tick is brought into the houses, and women and children are more frequently infected.

The spring and early summer months, when the ticks are most active, are the months of highest incidence in most places, but at higher altitudes, the infection season extends late into the summer, and even on into the autumn.

The intensity of the disease varies very considerably in different districts; in the Bitter Root valley and other districts in Montana, the death rate has been as high as 80 per cent, and, taking it all round, it is certainly 40 per cent in the mountain districts; but in some of the districts in the eastern states, where *Dermacentor variabilis* is the transmitter, it is much lower, and the average death rate is probably less than 25 per cent. In some districts there has been a decrease in the severity of the disease, whereas in others a very distinct increase in the severity and mortality has been observed in the last few years, *e.g.* in Idaho where the mortality a few years ago was said to be as low as 5 per cent and is at present about 30 per cent.

Pathology.—As in the classical disease, the rickettsiæ invade the endothelial cells of the smaller blood vessels, but in this infection thrombo-necrosis is the reaction rather than proliferative endarteritis. Of the macroscopic lesions, extensive ecchymoses into the skin, mucous membranes, and serous cavities, enlargement of the spleen, meningeal congestion, broncho-pneumonia, and scrotal gangrene are common.

In the blood there are no characteristic changes; there is usually a moderate leucocytosis, but a leucopenia (granulopenia) is not uncommon. The urine is acid; it is often reduced in amount, and retention may occur. Some albumin may be present.

SYMPTOMATOLOGY

The incubation period is from three to twelve days, being shorter in the more severe infections; after a day or so of prodromal symptoms, headache, backache, general malaise, and loss of appetite, the onset is rapid, though not usually as sudden as in classical typhus, with rigor and sweating, nausea and vomiting, photophobia, congestion of the conjunctivæ, intensification of the prodromal symptoms, and pains all over the body. The clinical picture then rapidly develops into that of a severe typhus attack (*vide supra*).

The temperature rises by rapid steps to a maximum between 103°F. and 106°F., according to the severity of the attack, in five or six days, it maintains its height for a few days often with deep remissions, and then begins to come down by lysis, taking three to four days in the eastern type and seven to eight in the more severe western type, the whole febrile period lasting from two to three weeks. Fatal hyperpyrexia with temperature above 108°F. sometimes occurs.

The rash usually appears from the second to the fourth day but may be delayed to the fifth or even sixth, and is sometimes preceded by a subcuticular mottling of the skin. The typical rash is bright red, macular or maculo-papular; it appears first on the wrist and ankles, sometimes on the forehead or back; it spreads rapidly all over the body including the palms and soles. In severe cases it commences with small pin-head ~~-----~~

that rapidly darken, and eventually become hæmorrhagic and coalesce. In the less severe cases, the spots appear in a succession of crops at a few days' interval. The rash fades slowly, leaving a brown stain which is very photosensitive and becomes red on exposure.

The pulse is full and bounding and often disproportionately slow in the mild cases, but in the toxic cases it becomes very rapid and is often uncountable.

Convalescence is usually slow and it may take some months.

The common complications are pneumonia, phlebitis, and hæmorrhages, including cerebral rarely, and, less frequently, iritis and acute nephritis.

Sequelæ are not common, but neuroses, psychoses, and insomnia, deafness, impaired vision, anæmia, and myocardial weakness have been reported.

Diagnosis does not present any difficulties in a typical case, but the temperature may suggest typhoid; other conditions that will have to be considered are measles and other acute exanthemata, secondary syphilis, meningitis, and purpura hæmorrhagica.

The diagnosis can be confirmed by the Weil-Felix reaction; standard agglutinations against OX19 and/or OX2, of 1 in 320 or higher should be considered diagnostic: a positive agglutination but in a lower dilution may be expected late in the attack. By this test, there is no clear differentiation between this disease and either endemic or classical typhus, though the OX2 agglutination is usually higher in Rocky Mountain spotted fever.

Another laboratory test is the inoculation intraperitoneally into a guinea-pig of 1 c.cm. of blood taken from the patient during the febrile stage. In the severe types, there is a characteristic scrotal swelling which may lead to gangrene, but in milder types this may be fleeting or absent; there is always some febrile reaction, but this is less specific.

Prevention and treatment.—Personal prophylaxis includes protection against tick bites by means of suitable clothing, for example, riding breeches and boots; women should wear similar clothes. When there has been any chance of tick infection, the lower limbs and body should be inspected carefully, and, if a tick is found, this should be removed by touching it with kerosene, so that it lets go and falls off, and not by squeezing it and pulling it off. The bite should be touched with silver nitrate or pure carbolic. The tick does not transmit immediately, and by this means infection may be obviated.

In the districts where the dog tick is the carrier, dogs should be washed in some insecticidal solution to prevent ticks adhering to them, whenever they have been out hunting, and the inadvisability of allowing them to come into the house at all is obvious. Chickens are a protection as they eat the ticks, but are not susceptible.

Vaccination has now been practised for a number of years, and it has been shown that some considerable degree of protection is given. However, it is obvious that there is room for improvement in the vaccine, for many inoculated persons have died as the result of infection with the virulent western strain. This is probably largely a matter of dosage, and with the improved technique of the last few years, a better vaccine should be forthcoming.

Vaccination is worth undertaking in severe endemic areas, but at present it only produces partial immunity for a comparatively short time, so that re-inoculation is indicated each season or whenever going on a hunting or other expedition in the endemic area (*vide supra*).

Treatment is symptomatic and does not differ from that of classical typhus. No known drugs are of any value.

ASSOCIATED DISEASES

Associated diseases include the tick-bite fever of southern Africa, the Transvaal, Natal, the Cape Province, and South and North Rhodesia, which is caused by a rickettsia, apparently of this group. A number of ticks have been incriminated as vectors, *e.g.* *Amblyomma hebraeum*, *Rhipicephalus appendiculatus*, *Boophilus decoloratus*, and *Hæmaphysalis leachi*. In the last-named, hereditary transmission for a number of generations has been proved. The reservoir of infection, if such exists, is presumably a veldt rodent, and cattle and dogs act as conveyors of ticks to the vicinity of man. The infection is transmitted by the bite, through an abrasion, or *via* the conjunctiva, in the latter case from contamination from a squashed tick. Clinically, it is usually a mild infection with a low death rate, less than 1 per cent. There may be an initial lesion of the *tache-noire* type, and there is usually a rash about the fifth day. The fever lasts about 14 days and ends by rapid lysis. In elderly patients, femoral thrombosis appears to be a common complication; pulmonary thrombosis has also been reported. The Weil-Felix reaction shows a late development—after the 10th day—and is positive with OX2 and OX19 antigen in moderately high titre, the former being higher than the latter, usually (*vide* Gear, 1940).

Fievre boutonneuse (*v.s.*) which occurs in the south of France and along the north African coast is caused by *Rickettsia conori* which is probably identical with *R. rickettsi*; it is transmitted from the dog, which may act as a reservoir of infection, by the dog tick, *Rhipicephalus sanguineus*; it is a comparatively mild form of typhus with a low mortality (2 per cent); there is an initial lesion—the *tache noire*—which is similar to that of tsutsugamushi disease (*v.i.*), but antigenically the disease is more closely related to Rocky Mountain spotted fever. The serum agglutinates proteus OX19 and OX2.

In São Paulo typhus of Brazil, the infection is transmitted by the tick, *Amblyomma cajennense*, possibly from a rodent reservoir. It is a severe disease with a high mortality (70 per cent) and similar both clinically and antigenically to Rocky Mountain spotted fever.

TSUTSUGAMUSHI

Definition.—Tsutsugamushi, or Japanese river fever, is a disease of the typhus group caused by *Rickettsia orientalis*, transmitted to man by the bite of certain mites, *e.g.* *Trombicula akamushi*, from field mice, rats, and other wild rodents; it is characterized by an initial lesion, and adenitis, and it runs a severe course; the serum of the patient agglutinates the proteus organism OXK.

Geographical distribution.—The original disease, as the name suggests, was described as occurring along the rivers of north Japan and in Formosa; since then it has been shown to have a much wider distribution, how wide we probably do not know even to-day. The disease that has been described as 'scrub' or rural typhus in Malaya; the coastal fever of Queensland, and

the pseudo-typhus of Sumatra are certainly the same disease. A similar disease is also reported from Indo-China and the Philippine Islands.

ÆTIOLOGY

The virus.—The causal organism is *Rickettsia orientalis* (*R. nipponica* or *R. tsutsugamushi*). This species is far more refractory to laboratory propagation than the other species of rickettsia. Infection is established only with considerable difficulty in guinea-pigs, after lowering their natural

resistance, but it can be transmitted to rabbits by intra-ocular injection, and to monkeys and apes by intradermal inoculation, with considerable regularity; in the latter it produces a primary ulcer, a febrile reaction, leucopenia, and agglutinins against OXK.

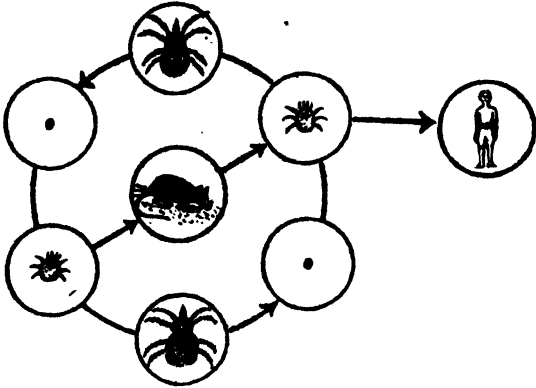


Figure 79: Transmission cycle in tsutsugamushi disease.

Laelaps australiensis. The larval mites, which only take one blood meal, become infected from field rodents, (e.g. in Japan the vole *Microtus montebelli*), transmit the infection to their offspring, and the larval mites of the next generation pass it on to man by their bite (salivary gland infection). The small mite, measuring only 0.25 mm., is barely visible to the naked eye, and, being easily overlooked, remains *in situ* for several days. The infection from this small insect is a very superficial one and therefore causes a local lesion; it is suggested that the absence of a local lesion in certain cases indicates that sometimes a large vector, whose proboscis reaches the deeper layers of the skin, is responsible.

Immunity.—Cross-protection tests with guinea-pigs, rabbits and monkeys show complete reciprocal cross-immunity between the Malayan and the Japanese type of tsutsugamushi, but not between this and other typhuses. The specific proteus is the OXK.

Epidemiology.—The disease is an endemic one, depending on the presence of the reservoir of infection and the transmitting mites. It occurs almost exclusively amongst farmers and other field workers, surveyors, game wardens and hunters. In Malaya, practically all persons infected had been in the habit of walking through the long *alang* grass and were mostly workers on oil-palm estates, especially those who worked around the roots of the trees where rats forage for food.

The disease occurs mainly amongst adult men, on account of their occupational associations, but probably for no other reason, as it is found amongst children doing similar work; persons of all races are apparently equally susceptible but the initial lesion and the rash are more difficult to identify on the dark skin.

In Japan, the disease occurs most frequently between June and October, but, in Malaya, it occurs all the year round.

Pathology.—This does not differ materially from that of other typhus fevers. In Malaya, Lewthwaite and Savor (1940) found characteristic changes in five out of seven brains examined microscopically. Macroscopically, in 12 post-mortem examinations, they found extensive subdural hæmorrhages in two cases, 11 enlarged spleens of which eight were diffuent, enlarged lymphatic glands in 10, and petechial hæmorrhages in the heart in four, in the pleura in 11, and in the kidneys in five cases.

The blood shows a leucopenia or a normal leucocyte count, very rarely a slight leucocytosis. There is an actual or relative increase of lymphocytes, a slight increase of monocytes, a granulopenia, and usually complete absence of eosinophils. The urine shows traces of albumin, and the usual characters associated with fever.

SYMPTOMATOLOGY

The incubation period in this infection varies over a wide range, from 5 to 21 days. The onset is usually sudden, all symptoms developing within 24 hours, but occasionally there is a prodromal period lasting a few days with a slight headache and malaise; the first definite symptoms are almost invariably fever, shivering, and headache, often with vomiting and pains all over the body; there is photophobia and suffusion of the eyes and some injection of the conjunctivæ. Cough may be distressing, even without the development of lung complications. The symptoms are not at first severe, but develop steadily in intensity up to the end of the first week and longer, and continue to be severe during the rest of the febrile period, Prostration continues to increase and a state of intense toxæmia may develop.

The initial lesion that occurs at the site of the bite was at one time supposed to be a *sine qua non* for the diagnosis of this form of typhus, but it is obviously very variable, both in its incidence and character; it may well be dependent on some factor other than the rickettsial infection, which varies in different localities as well as in different species of vector. In Japan and Sumatra, it is apparently very common; in Malaya, it is rarely found. The lesion is at first macular, then papular, and eventually a necrotic centre develops which separates and leaves a punched-out ulcer. It is very probable that in a number of cases it does not go beyond the macular or papular stages, and heals before the main symptoms develop. That it is noticeably more common in fair-skinned individuals adds support to this suggestion.



Temperature chart in typhus with an initial lesion (see plate X, figure 4).

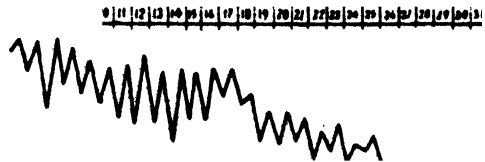
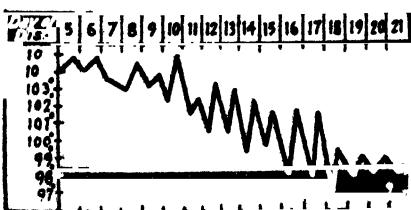


Figure 81 : Temperature charts in tsutsugamushi disease (after Nagayo, 1923).

The typical lesion at the time of onset of general symptoms is a depressed necrotic eschar about 5 mm. in diameter with a well-defined areola of about the same breadth.

The fever usually rises rapidly to 101 or 102°F., and then after a further few days reaches its maximum of 104° or higher, and is maintained at this level with deep morning remissions of two or three degrees, until the end of the second week, when it falls by rapid lysis; after this there may be one or two final kicks in the temperature chart up to 100° or 101°, during the next day or so, before the fever finally subsides. In the Japanese type, the lysis may take several days and a low fever may continue for another week. As in other typhuses, the height of the fever is not a guide to the severity of the infection.

The pulse rate is usually increased with the temperature, though a few cases in which it remained slow have been reported; in convalescence there may be bradycardia.

The rash appears about the fourth or fifth day, but in some cases there is a subcuticular mottling from the second day. The rash proper is macular with barely perceptible papules in a few cases; it is dusky red, discrete and fades on pressure; it appears on the chest, abdomen and flanks, and spreads to the limbs and occasionally the face; it begins to fade after about three days, and leaves no stain. The rash is not however as constant or as marked as in classical typhus or Rocky Mountain spotted fever.

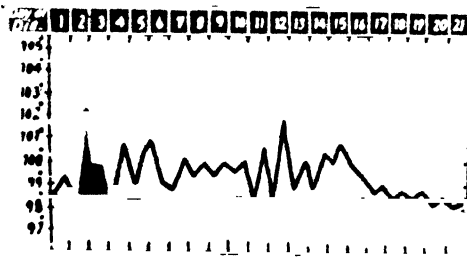


Figure 82 : Temperature chart of a case of 'scrub' typhus in Malaya (Anigstein, 1933).

The lymphatic glands, especially—but not only—those that drain the initial lesion, are palpably enlarged in about half the cases, and are often tender (*see Pathology*). The spleen is frequently palpable and tender.

Nervous symptoms are usually pronounced, and develop as the temperature rises; there are fine tremors of the lips and tongue, and twitchings of the face muscles; the patient is dull and apathetic during the day and often delirious at night; insomnia is common; he may become stuporous and eventually pass into coma. Another symptom is deafness; this is irregular but tends to develop throughout the disease.

Complications.—The only frequent complications are bronchitis and broncho-pneumonia.

Diagnosis.—The finding of the initial lesions, or even of the remains of such lesions, is not essential for a diagnosis of this type of typhus, though this constitutes the only really characteristic clinical feature; others are the enlarged glands, and the leucopenia with an increase in lymphocytes.

The Weil-Felix reaction gives agglutination in high titre against proteus OXK, and a negligible agglutination with OX19 and OX2. The lowest titre that can be accepted as diagnostic is 1 in 250, but, as a few cases of leptospirosis have shown even higher agglutinations against OXK proteus, diagnosis on this titre should be confirmed by subsequent tests to demonstrate a rising and then a falling titre. Further confirmation may be obtained by guinea-pig inoculation, as in this disease the guinea-pig is refractory and, even if infection is established, there is no scrotal swelling.

In the absence of laboratory facilities, epidemiological observations provide better grounds than the clinical for the differentiation of the typhuses.

Prevention and treatment.—The adoption of suitable clothing when in endemic areas and careful inspection of the body after removing the clothes are obvious measures for personal protection. Prophylactic inoculation is being developed for this, as well as for other, typhuses. In special circumstances, rodent extermination may be advisable where the specific reservoir has been identified, but such a measure should not be advocated lightly.

Prognosis.—The infection is less severe in children and very fatal in old people. In Japan, the death rate is given as 30 to 60 per cent, and, in Malaya, as an average of 15 per cent.

'Q' FEVER

The most recent recruits to the typhus fevers, are the so-called 'Q' fever, first reported from Brisbane (Derrick, 1937), and the American 'Q' fever, which takes the form of a pneumonitis; these two diseases appear to be caused by antigenically-identical rickettsiæ.

The Australian disease is confined almost entirely to abattoir and dairy workers, except that many laboratory infections have occurred.

The Queensland bandicoot, *Isodon torosus*, provides a reservoir of infection and the infection is transmitted from rat to rat by the tick, *Hamaphysalis humerosa*, in which this rickettsia is possibly a natural infection. Another common ectoparasite of the bandicoot is *Ixodes holocyclus*, which is a very promiscuous insect and feeds also on cattle, dogs and man; this tick is a potential vector of rickettsiæ, and it seems very probable that it conveys the infection to young cattle (known to be susceptible); these in turn infect the common cattle tick, *Boophilus annulatus*, which broadcasts the infection. There are steps in this cycle of infection that still have to be confirmed, especially with regard to the part played by *Ixodes holocyclus*, but it would appear to be as shown graphically below :—

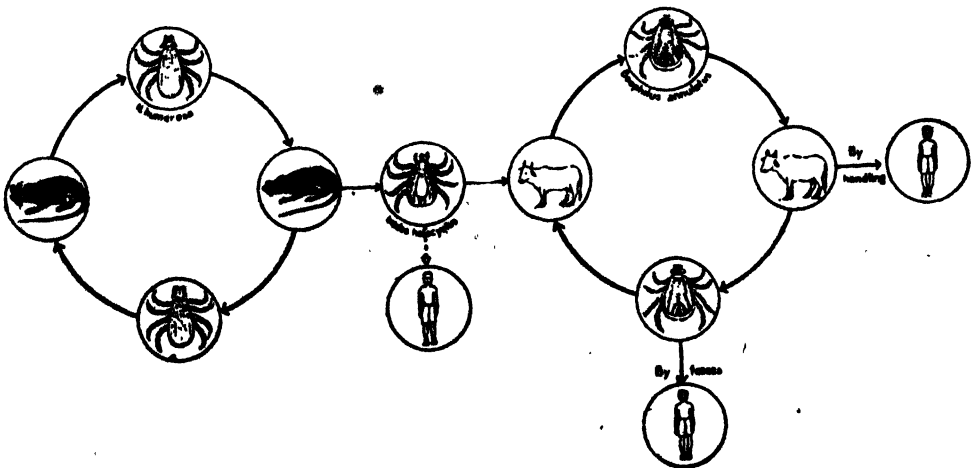


Figure 83 : Probable transmission cycles in Australian 'Q' fever.

The causal organism. *Rickettsia burneti*, infects the endothelial cells lining the alimentary canals of the susceptible ticks. The rickettsiæ

multiply in these cells, which eventually burst into the lumen of the alimentary canal, and the rickettsiæ are passed out with the fæces.

Infection may take place by the handling of the cattle harbouring infected ticks, from the tick fæces, or from crushed ticks, but there is strong epidemiological evidence that the main route of invasion is *via* the lungs, from the infected dust of the abattoirs (e.g. infection has been reported in casual visitors to abattoirs).

The infection is transmissible to guinea-pigs, monkeys and other domestic and laboratory animals, but mice appear to be most susceptible and from their livers and spleens large numbers of rickettsiæ can be recovered, with which agglutination tests can be carried out.

Immunity develops in an infected person or animal, and their serum will agglutinate the rickettsial emulsions. There is cross-immunity against the rickettsia that causes American 'Q' fever, but not against any other rickettsia, e.g. *R. rickettsi* or *R. prowazeki*. No agglutination occurs with any of the recognized proteus X strains.

The clinical picture is that of a mild form of typhus with a low mortality; in the typical case the onset is sudden, the fever rises to as high as 104°F., with deep remissions, it lasts for about a week, and then falls by crisis. There is another form in which the fever runs a more chronic course; other symptoms are intense persistent headache, photophobia and conjunctival congestion. There is usually marked bradycardia. There is no rash.

The American form of 'Q' fever has an interesting history in that it was an example of a disease in which the causal organism was discovered before the disease. A rickettsia, which was antigenically different from *Rickettsia rickettsi*, the causal organism of Rocky Mountain spotted fever, was isolated by Davis and Cox (1938) from the tick, *Dermacentor andersoni*, in Montana. This organism caused an outbreak of pneumonitis amongst the staff in the laboratory where it was being experimented with, and it was also isolated from persons, similarly with pneumonitis, who had acquired the infection naturally, possibly from ticks.

In the case of the laboratory infections, many persons, of whom one died, who had had no direct contact with the cultures or infected animals, were infected, so that it seems probable that the infection was air-borne, possibly spread by dust.

The causal organism of this American 'Q' fever was called *Rickettsia diaporica* but it has been shown to be antigenically identical with *R. burneti* which has precedence.

The position of this disease *vis-à-vis* other typhuses is not yet clear. It does not appear to conform to any of the types included in the provisional classification given above; it exhibits few clinical or other features common to the previously recognized typhuses; and the causal organism, though a rickettsia, differs from all the other known rickettsiæ in its pathogenicity to animals and in its antigenic structure.

TYPHUS FEVER IN INDIA

Introductory.—Attention was first drawn to this disease in India by Megaw (1917) who described a case of typhus-like fever that had occurred in the Kumaon hills; he insisted on the clinical similarity between the case he was reporting and typhus, and he strongly suspected that the transmitter was a tick (he was himself the patient). The importance of

this observation will be realized if we remember that at this date no form of tropical typhus had been recognized as such, and little was known about any of the non-epidemic typhuses. Megaw later described other cases of typhus occurring in India, in which the patients had been bitten by unidentified ticks; in other cases, though there was no direct history of a tick bite, the possibility could not be excluded.

Since this date, a number of cases of typhus and suspected typhus have been reported from various parts of India. The most important publication on the subject is that of Boyd (1935) who collected data from 110 cases that had occurred in the army, or in persons associated with the army, in the previous year. This is another demonstration of the value of such a body of individuals as the army in India as detectors of inapparent diseases amongst the indigenous population; the individuals, even when they are not British born, are usually foreign to the locality and therefore have none of the natural immunity that the indigenous population enjoys. One important point in Boyd's paper was that he was unable in any single case to identify the vector, and in many there seemed to be a reasonable doubt if any of the previously recognized insect vectors were involved.

Some experimental work has been done in India, but the position has not been appreciably clarified by this; it has been mainly concerned with the agglutinating properties, against the proteus X strains, of the blood of various animals suspected as reservoirs of infection, and with the isolation of rickettsial strains from these and from possible arthropod vectors. Competent research workers have been engaged in these investigations, and the inconclusive results that have been produced are due to the circumstances, mainly the extremely sporadic nature of the disease in this vast country, though the annual incidence probably runs into tens of thousands of even clinically apparent cases. A murine strain has been isolated from rats a number of times, and this has been transmitted by rat fleas; and a tsutsugamushi (XK) strain has been isolated from a patient. The monkeys of the Simla hills (*Silenus rhesus*) have been suspected as a reservoir of infection, they have been found to be infested with *Trombicula deliensis*, and their blood has been shown to agglutinate OXK at a dilution of 1 in 50 in 32 per cent of instances, and at a dilution of 1 in 25 in nearly all others, whereas the plains monkeys, not so infested, give a much lower grade of agglutination.

The only possible view to take of the position is that, in a vast country like India, with almost every possible climate represented, it would be very surprising if there were only one type of typhus. A more reasonable hypothesis is that each of the major groups is almost certainly represented; our object should be to sort them out and attribute to each its special clinical picture, its vector, and its reservoir of infection, so that they can be recognized and appropriate measures of prevention can be adopted, rather than to stress their similarity—beyond the fact that they are typhus fevers—and to claim for them homogeneity.

The fortunate accident of the close antigenic relationship of the different rickettsiae to certain specific strains of proteus will serve us for the time being as a means of separating the various typhus fevers, until this artificial method is replaced by the more specific methods of agglutination with rickettsial emulsions and of infection and cross-immunity experiments with laboratory animals; such methods are now being employed extensively in other countries, for example the U.S.A. and Malaya, and, when the technique becomes more standardized, will undoubtedly be adopted, to a

greater extent than they have been in the past, by investigators in India. Meanwhile, it is important that clinicians should make themselves familiar with the clinical pictures in the different types of typhus that occur in other countries, so that they will recognize them when they encounter similar diseases in India, and that bacteriologists should include the proteus group of organisms in their Widal tests, even when physicians do not ask for this test specifically.

Classification.—At the present date, Boyd's classification of the typhuses of India is the only one worth quoting; this classification has its strict limitation, as Boyd would be the first to admit, and it is to be hoped that it will soon be replaced by a more satisfactory one. Boyd's classification with certain important clinical and other data is given in the table below :—

TABLE III

Type	XK	X2	X19	
			Poona-Ahmed-nagar	Bangalore
<i>Geographical distribution.</i>	Northern, Eastern and Southern Commands except Poona-Ahmed-nagar area and Madras District. Not reported from Western Command.	Deccan District and Poona Independent Brigade Area only.	Deccan District, C. P., and Poona Independent Brigade Area only.	Southern Command except Poona Independent Brigade Area and Ahmed-nagar vicinity.
<i>Seasonal incidence : maximum months.</i>	August and September.	December	December	More or less evenly spread, except February, March and April.
<i>Rash :—</i>				
Number of cases. { British { Indian	15/21 1/14	8/8 5/6	10/10 6/6	5/6 1/21
Day of appearance. { British { Indian	5th or 6th 7th	3rd or 4th	3rd	4th to 10th 8th
Type ..	Flush : macules	Macules; papules; petechial.	Macules; papules; petechial.	Maculo-papular.
Distribution ..	Trunk only	Generalized	Generalized	Trunk and limbs.
Duration in days. { British { Indian	7	{ 18.4 { 14.4	25 10.5	4 3
Staining	Nil	In some cases	In some cases	
Average duration of pyrexia in days.	14.2	12.5	15.5	10.4
Average stay in hospital, in days.	31	27.5	29.5	24.6
Proteus agglutinins. { XK { X2 { X19	+++ — —	± +++ +	± ± + to ++	± ± +++

Epidemiology.—In most of Megaw's cases there was a clear association with the open country and the chance of contact with its fauna, but in many of Boyd's series no such history was given, and some soldiers who developed typhus had even been confined to barracks for a considerable time. Many reports recently received have been of cases amongst town residents.

Symptomatology.—It would not be advisable to attempt to correlate the clinical findings of different observers, as they are probably descriptions of more than one disease. Therefore two classical descriptions are given more or less verbatim; Megaw (1917) described his case as follows :—

The first symptoms were malaise and headache, which gradually increased until the fourth day. The headache was referred to the orbits just above the eye-balls, and from the fourth day it steadily subsided. The only other symptoms were weakness and some pain and discomfort in the muscles of the back which caused disturbance of sleep for two or three nights.

On the fifth day a diffuse macular erythema was noticed all over the body including the palms and soles and the face. In the neighbourhood of each spot there was at first swelling and tenderness of the skin, so that flexion of the fingers was painful.

In a day or two, the eruption became more pronounced, the colour changing to brownish red; about the eighth day the spots had a distinct tendency to be petechial, and by this time the swelling and tenderness had disappeared. The eruption faded rapidly with the fall of the temperature, but a brown staining at the site of the spots was visible for about five weeks afterwards.

On the front of the right thigh, where the spots were readily observed, and where there was an average crop, there were 21 spots, roughly circular in shape and merging gradually into the surrounding skin. They varied in size from about three to seven millimetres in diameter; at first they disappeared on pressure; but later, when they became petechial, they ceased to do so.

There were no symptoms referable to the respiratory or nervous system, and the patient took a keen interest in the progress of his case. Convalescence was rapid; he got up from bed on the day on which the temperature fell to normal, and ten days later was in his usual good health.

The leucocyte count on the tenth day was 15,400 per c.mm.

Boyd (1935) described the clinical picture of the most important group, **XX**, in his classification, as follows :—

Severe headache was a very constant and early symptom. The face was usually flushed, and the conjunctivæ somewhat injected. Rigors and sweats were common in the early stages, and toxæmia, with its accompanying symptoms of lassitude and drowsiness, was of varying severity. Severe pains in the joints, or 'all over the body', occurred in several cases.

The rash was by no means a constant feature, being present in only 15 of the 21 British cases, and in only 1 of the 14 Indian cases. It usually appeared on the fifth or sixth day, but was recorded as early as the first and as late as the eighth day of illness.

The rash appears on the fifth day of the disease. A flush may be present on the fourth day. This may be demonstrated on an apparently normal skin by the pressure of the hand. The paler impression produced by the palm and fingers persists on the skin. The rash is that of true typhus, though the lenticular papules have not been observed. It is a dusky erythema, with scattered irregular blotchy underlying macules, purple in colour. The macules persist on pressure in some degree, while the flush fades, leaving the skin very pale by contrast. In severe rashes the macules sometimes appear raised but cannot be felt. The rash is best seen in the umbilical and epigastric areas, and over the lower ribs. It extends to the sides of the thorax. The distribution of the flush is wider, it is well marked over the trunk, with the exception of the upper part of the front of the thorax, and the hypogastric and iliac areas. It is particularly well seen on the back and between the shoulder blades. The rash has been seen on the upper and lower limbs, but usually these are not affected. It is not very striking in appearance and may not be noticed. It fades gradually, the flush disappearing earlier than the macules. As a rule it is no longer visible at the termination of the pyrexia.

It is worthy of note that in no case of this series did the rash become papular or petechial, nor, with one exception, did the macules extend beyond the trunk. The macules were found chiefly on the abdomen and thorax; the face and neck and extremities were unaffected.

The inconspicuous nature of the rash no doubt affords the explanation of its apparent rarity in Indian patients, as it is presumably obscured by the pigmented skin.

The average duration of the rash, calculated from figures given in thirteen cases, was seven days. There was, however, difficulty in determining the exact time when it could be said to have disappeared.

Complications and sequelæ were by no means uncommon. Nine cases showed pulmonary symptoms, 5 developing bronchitis, 2 pneumonic symptoms, and 2 pleurisy. Three cases developed acute mental symptoms, and 2 others varying degrees of transient paralysis.

The average duration of fever (33 cases) was 14.2 days. During the pyrexial period the pulse rate was relatively slow, resembling in this respect the pulse in fevers of the enteric group.

Recovery was by lysis, and in some cases by crisis. In uncomplicated cases all other symptoms disappeared and convalescence was rapid as soon as the fever subsided.

The average stay in hospital (35 cases) was thirty-one days.

Recent observations.—A few notes are added on three recent reports on outbreaks of Indian typhus fevers.

Heilig and Naidu (1942) reported 14 cases in Indians in Mysore, from the city and surrounding country. All the cases were sporadic, they occurred between August and February, and there were no indications regarding the transmitting agent. The onset was sudden, but without rigor,

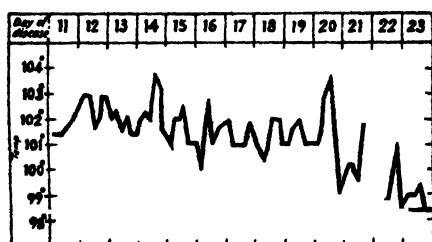


Figure 84 : Temperature chart of a case of Indian endemic typhus.

with malaise, headache, photophobia, body aches, and usually conjunctival suffusion. No splenic enlargement was noted. The temperature chart showed a moderately high remittent fever which lasted from 16 to 21 days and resolved by rapid lysis (see figure 84). The rash first appeared between the fifth and the tenth days; it started as a pinkish macular rash on the trunk and upper extremities, and it spread all over the body, and to the lower part of the face in a few cases. The rash became maculo-papular, the pink colour changing to purplish, and then petechial; desquamation occurred during the fourth week; and, finally, it turned to brown and left a stain that persisted for months. There was a distinct leucocytosis in most cases.

The diagnosis depended on the demonstration of rickettsiæ in the tunica vaginalis of guinea-pigs injected with the blood of some of the cases, but in only one case was a Neill-Mooser reaction produced in the injected guinea-pig.

The Weil-Felix reaction was positive with the OX2 antigen in most of the cases, though there was some co-agglutination with the other two antigens.

PLATE X

Fig. 1.—A case of Indian typhus (proteus agglutinations negative): 2nd day of rash, 11th day of disease.

Fig. 2.—Same patient as in figure 1 : 29th day of disease.

Fig. 3.—Same as figure 2.

Fig. 4.—Another similar case : rash appeared on 10th day.

(After Heilig and Naidu, 1941, 1942.)

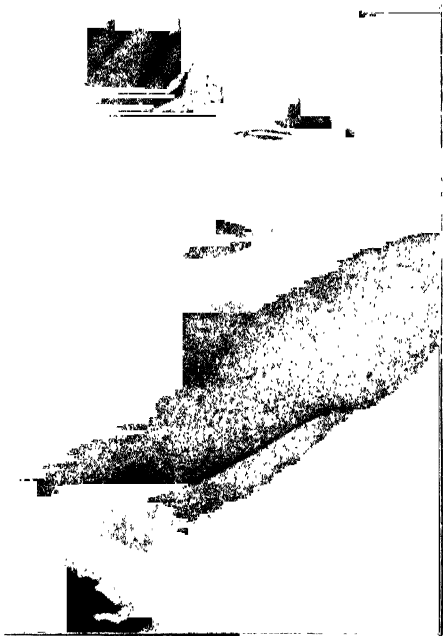


Fig. 1



Fig. 2



Fig. 3

PLATE XI

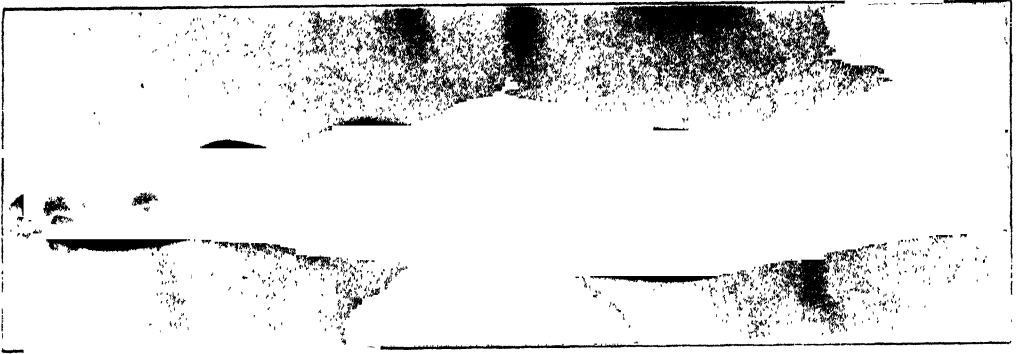


Fig. 1.—Rash in Indian typhus (after Heilig and Naidu, 1941).



Fig. 2.—Neill-Mooser reaction (after Heilig and Naidu, 1941).

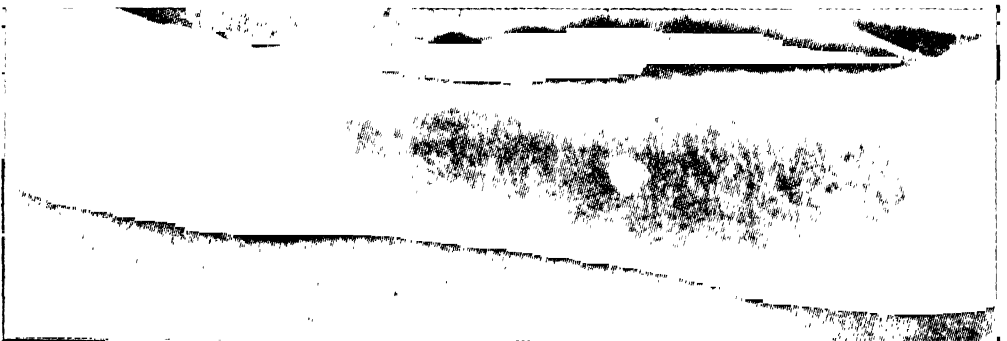


Fig. 3.—Primary ulcer in a case of Malayan scrub (XK) typhus (after Fletcher and Field, 1929).

A second report was from a military hospital (personal communication from Lieut.-Colonel T. A. A. Hunter, R.A.M.C.). The patients were eleven British soldiers, who had been in camp near Bombay during the month of November; the symptoms developed in one case 17 days after arrival at the camp, and in another 10 days after leaving it, so that if infection took place in the camp—an almost inevitable conclusion—the incubation period was between 10 and 17 days; but there was no history of tick bite in any case. Eight cases occurred in one battalion.

The onset and the course of the disease was very similar to that of the Mysore cases; but the symptoms were exceptionally mild; the fever was also of the same nature and lasted from 13 to 16 days. The rash was also a marked feature in this series, but developed within 24 hours of the onset of symptoms in every case and in two was the first evidence of the disease; it developed in the lower extremities first and spread rapidly all over the body except the face. This early development of the rash constituted the only striking difference between the two series.

The Weil-Felix was positive with the OX2 antigen in six cases, but in no case was a positive Neill-Mooser reaction produced in injected guinea-pigs.

These two series have a number of features common with Boyd's X2 group (*see table III*), but the difference in the time of appearance of the rash is interesting. There is no clue in either case to the transmission problem.

A third outbreak occurred in Calcutta in the autumn of 1942. The patients were again British soldiers. The symptoms were more severe than is usual in this country, and in sixteen definite cases two deaths occurred. The rash was well developed in nearly all of them. The temperature charts were very like the classical typhus chart; three are shown in figure 85. The majority of these cases showed a significant agglutination reaction with the OXK strain of proteus, but in one case with OX2.

Eight of the patients were from one regiment and were living in a large building in a relatively densely populated part of Calcutta. No clue could be obtained as to the nature of the vector, or to the source of infection; none of the patients was louse-infected.

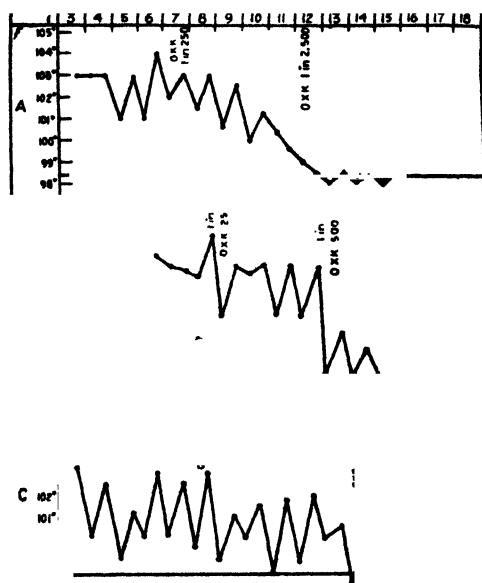


Figure 85: Temperature charts in three Calcutta cases of typhus.

Conclusion.—The position in India is that we know that the disease exists and that it is widespread. We must endeavour to find out the extent of its incidence and whether or not it can be considered a serious public-health problem, and whether it is increasing. We have the example of the U.S.A. where during the last decade endemic typhus has apparently

increased ten-fold, and Rocky Mountain fever has spread from the western states to the east coast. We must use the Weil-Felix test to help us to identify the disease, but we should be careful not to accept the indications of the test without clinical support, or the confirmation of animal experiments. The Weil-Felix test is after all a non-specific test, and it is possible that there are certain non-rickettsial diseases caused by organisms with which one or other of the known proteus X strains is antigenically related.

REFERENCES

- ANDERSON, J. F., and GOLDBERGER, J. Relation of so-called Brill's Disease to Typhus (1912). *Pub. Health Rep.*, **27**, 149.
- ANIGSTEIN, L. (1933) Researches on Tropical Typhus. *Studies, Inst. Med. Res., F. M. S.*, No. 22. Kyle, Palmer and Co., Ltd., Kuala Lumpur.
- BOYD, J. S. K. (1935) Fevers of the Typhus Group in India. *J. Roy. Army Med. Corps*, **65**, 289, 361.
- BRILL, N. E. (1898) A Study of Seventeen Cases of a Disease Clinically Resembling Typhoid Fever, but without the Widal Reaction. *New York Med. J.*, **67**, 48 and 77.
- BURNET, F. M., and FREEMAN, M. Experimental Studies on the Virus of 'Q' (1937). *Med. J. Australia*, **ii**, 299.
- BYAM, W. (1923) Trench Fever. *Byam and Archibald's Practice of Medicine in the Tropics*, **3**, 2114. Henry Frowde and Hodder and Stoughton, London.
- DAVIS, G. E., and COX, H. R. (1938). A Filter-passing Infectious Agent isolated from Ticks. Isolation from *Dermacentor andersoni*, Reactions in Animals, and Filtration Experiments. *Pub. Health Rep.*, **53**, 2259.
- DERRICK, E. H. (1937) 'Q' Fever a New Fever Entity: Clinical Features, Diagnosis and Laboratory Investigation. *Med. J. Australia*, **ii**, 281.
- DURAND, P., and SPARROW, H. (1940). Inoculation Pulmonaire des Virus Typhiques et Boutonneux. *Compt. Rend. Acad. Sci.*, **210**, 420. (Abstract—*Trop. Dis. Bull.*, **37**, 572.)
- DYER, R. E. (1941) The Charles Franklin Craig Lecture for 1940: The Control of Typhus Fever. *Amer. J. Trop. Med.*, **21**, 163.
- DYER, R. E. *et al.* (1931) Experimental Transmission of Endemic Typhus Fever of United States by Rat Flea (*Xenopsylla cheopis*). *Pub. Health Rep.*, **46**, 2415.
- FLETCHER, W., and FIELD, J. W. The Tsutsugamushi Disease in the Federated (1927). *Bull. Inst. Med. Res., F. M. S.*, No. 1. John Bale, Sons and Danielsson, Ltd., London.
- FLETCHER, W., and LESSLAR, J. E. Tropical Typhus in the Federated Malay (1925). *Bull. Inst. Med. Res., F. M. S.*, No. 2. John Bale, Sons and Danielsson, Ltd., London.
- GEAR, J. (1940) Vaccination Against Typhus Fever. *South African Med. J.*, **14**, 476.
- GERHARD, W. W. (1837) On the Typhus Fever, which occurred at Philadelphia in the Spring and Summer of 1836. *Amer. J. Med. Sci.*, **10**, 289.
- HEILIG, R., and NAMBU, V. R. (1941). Endemic Typhus in Mysore. *Indian Med.*
- Idem* (1942). Further Experiences on Endemic Typhus in Mysore. *Indian Med. Gaz.*, **77**, 338.

- LEWTHWAITE, R., and SAVOOR, S. R. Rickettsia Diseases of Malaya; Identity of (1940).
Tsutsugamushi and Rural Typhus. *Lancet*, *i*, 255 and 305.
- MAXCY, K. F. (1926) .. Epidemiological Study of Endemic Typhus (Brill's Disease) in South-Eastern United States. *Pub. Health Rep.*, **41**, 2967.
- MEGAW, J. W. D. (1917) .. A Case of Fever Resembling Brill's Disease. *Indian Med. Gaz.*, **52**, 15.
- NAGATO, M. (1923) .. The Tsutsugamushi Disease or Japanese River Fever. *Byam and Archibald's Practice of Medicine in the Tropics*, **3**, 2134. Henry Frowde and Hodder and Stoughton, London.
- NAPIER, L. E. (1919) .. The Weil-Felix Reaction in a Mild Epidemic of Typhus. *Lancet*, *ii*, 863.
- NICOLLE, C., and CONSEIL, E. (1911). Etiologie du Typhus Exanthematique. *Ann. Inst. Pasteur*, **25**, 109.
- RICKETTS, H. T. (1906) .. The Study of 'Rocky Mountain Spotted Fever' (Tick Fever?) by Means of Animal Inoculations. *J. Amer. Med. Assoc.*, **47**, 33.
- DA ROCHA-LIMA, H. (1916) .. Beobachtungen bei Flecktyphus-läusen. *Arch. Schiffs- u. Trop.-Hyg.*, **20**, 17.
- SELLARDS, A. W. (1923) .. The Cultivation of a Rickettsia-like Micro-organism from Tsutsu-Gamushi Disease. *Amer. J. Trop. Med.*, **3**, 529.
- STILLE, A. (1838) .. Table of Comparison between Typhus and Typhoid Fevers. Philadelphia.
- WEIGL, R. (1924) .. Active Typhus Immunity. *Med. Klin.*, **20**, 1046.
- WEIL, E., and FELIX, A. (1916) .. Zur serologischen Diagnose des Fleckfiebers. *Wien. Klin. Woch.*, **29**, 33 and 974.
- WILDER, R. M. (1911) .. The Problem of Transmission in Typhus Fever. *J. Inf. Dis.*, **9**, 9.
- WILSON, W. J. (1909) .. On Heterologous Agglutinins more particularly those present in the blood serum of Cerebro-spinal Fever and Typhus Fever Cases. *J. Hyg.*, **9**, 316.
- WOLBACH, S. B. (1919) .. Studies on Rocky Mountain Spotted Fever. *J. Med. Res.*, **41**, 1.
- Idem* (1923) .. Rocky Mountain Spotted Fever. *Byam and Archibald's Practice of Medicine in the Tropics*, **3**, 2092. Henry Frowde and Hodder and Stoughton, London.
- Idem* (1925) .. The Rickettsiæ and their Relationship to Disease. *J. Amer. Med. Assoc.*, **84**, 723.
- ZINSSER, H. (1934) .. Varieties of Typhus Virus and Epidemiology of American Form of European Typhus Fever (Brill's Disease). *Amer. J. Hyg.*, **20**, 513.
- ZINSSER, H., WEIL, H., and FITZ-PATRICK, F. (1937). Agar Slant Tissue Cultures of Typhus Rickettsiæ (both Types). *Proc. Soc. Exper. Biol. and Med.*, **37**, 604.

OROYA FEVER, OR BARTONELLOSIS

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Definition.—Oroya fever, or Carrion's disease, is a febrile disease with a very limited geographical distribution, occurring in certain valleys on the western slopes of the Andes in South America. It is caused by a bacillus-like micro-organism, *Bartonella bacilliformis*, which is probably transmitted from man to man by biting insects. It is variable in its severity, but may develop an acute and serious form in which there is extreme anæmia; a very common secondary manifestation is the granulomatous eruption previously known as verruga peruana.

Historical.—It is believed that the fatal disease which wrought havoc in Pizarro's army in the 16th century was Oroya fever.

Medical attention was first drawn to it in 1870, when, during the building of the railway to Oroya, 7,000 deaths occurred amongst imported labour. It was from this that the disease received its name, which is a misnomer as it does not actually occur in Oroya.

In 1885, Carrion, a medical student, inoculated himself from a verruga nodule and developed a fatal attack of Oroya fever. From this time local physicians have assumed that the fever and the subsequent eruption were manifestations of the same disease. The causal organism was identified by Barton in 1909, and his observations were confirmed by Strong and others in 1915.

The etiological identity of the two conditions was again questioned by the Harvard Commission in 1913, but Noguchi's cultural work re-established the claim for their identity and later Mayer, Borchardt, and Kikuth (1927) produced both the local lesions and the severe febrile disease with anæmia, the latter after splenectomy, in monkeys, by inoculation of material taken from a case of verruga peruana that arrived in Hamburg. These observations were confirmed by the Harvard Commission of 1937; in this instance, cultures were used for producing infections in monkeys.

EPIDEMIOLOGY

Geographical distribution.—It has a limited distribution in South America between 2°N. and 13°S. It occurs mainly in Peru, but recently indigenous cases have been reported from Bolivia, Ecuador and now Columbia. The area in Columbia is in the basin of the Guaitara river, a fertile area with 100,000 inhabitants; the death rate from this disease in the first eight months of 1938 amounted to 1,800 persons.

Other epidemiological features.—The disease is confined to certain valleys in the Andes, between 1,000 and 12,000 feet above sea level, in which sometimes every individual in the whole community is, or has been, infected. New-comers to these valleys almost invariably become infected and suffer the acute febrile attack, and frequently die.

The disease appears after the rainy season, when insect life is most abundant and malaria is rife.

Persons of all ages are affected but the disease is much milder in children, and is probably often unrecognized.

ÆTIOLOGY

The causal organism.—*Bartonella bacilliformis* has two forms, a small bacillus-like form, 1μ to 2μ in length, which may show branching, and an ovoid form about 1μ in mean diameter. It stains well with Romanowsky stains, taking a blue colour (see plate II, F).

It can be grown in Vervoort's medium used for the cultivation of leptospira, but does not grow easily. It is suggested that the different stains of *Bartonella* vary in their ability to grow in culture medium.

They are found in the red cells in the peripheral blood in an acute case, and in the endothelial cells of the capillaries in post-mortem or biopsy tissue.

Transmission.—The mode of transmission is not yet known, but many suggestions, some supported by experimental data, have been made. Sand-flies appear to be the most likely vectors. The disease has been produced in monkeys by the injection of crushed wild sand-flies, and sand-flies have been infected by feeding on a patient, but the complete human experiment has not yet been carried through. *Phlebotomus noguchi* and *P. verrucarum* occur in the endemic areas and are under the gravest suspicion as vectors. Other *Bartonella* species are transmitted by insects, e.g. *Bartonella canis* and *muris*, by the dog-flea and the rat-louse, respectively.

Sources of infection.—Man is probably the main source of infection. As bartonellæ are occasionally found in the peripheral blood in the absence of symptoms, or even some time after symptoms have subsided, it does not seem necessary to suggest an animal reservoir. However, rats and certain other wild animals are susceptible to infection and may conceivably act as reservoirs of infection, though none has so far been incriminated.

PATHOLOGY

The general reaction produced is the result of bartonella invasion of the arteriolar endothelium and reticulo-endothelial cells of the lymphatic tissues, and of the blood destruction; much red cell debris has to be disposed of, and there is very great anæmia.

Lymphatic glands are often enlarged, and the spleen usually, and there is a deposition of dark-yellow pigment in most of the organs, which gives the reactions of melanin. There are often petechial hæmorrhages in the mucous membranes and in some of the viscera.

The endothelial cells of the arterioles and lymphatic channels are invaded by the bartonellæ, and the lumens of the channels are often blocked, so that necrosis or œdema may occur. Necrotic areas are often seen in the spleen, and also in the liver, in the central part of the lobules.

The bone marrow shows a marked hyperplasia, both of the erythroblastic and the leucoblastic elements.

In the local lesions, there is blocking and dilatation of the vessels with the production of a hæmangiomatous condition. There is proliferation of the endothelial cells lining these blood sinuses; in these cells, bartonellæ may be found, but they are not numerous. There is much new blood-vessel formation. The lymph channels are also obstructed, and the blocked vessels are surrounded by an area of infiltration, in which lymphocytes, plasma cells, and fibroblasts take part.

Blood picture.—The red cell count may be reduced to less than a million. As is usual in these hæmolytic anæmias, the red cells are on the large side; with the appearance of reticulocytes, the picture will be definitely a pseudo-macrocytic one, and immature cells, such as normoblasts and erythroblasts, will appear in the blood.

The leucocytes will be increased, often up to 20,000 per c.mm., the proportions of the various types being maintained at about the normal.

SYMPTOMATOLOGY

Discussion.—The view that Oroya fever and verruga peruana are manifestations of the same infection is now generally accepted. There is considerable parallelism between this disease and kala-azar, a condition in which an acute visceral disease may be followed by a generalized dermal eruption.

In Oroya fever, if the patient dies from the acute febrile disease, he naturally does not suffer from the dermal lesions; if he has a very severe febrile attack but recovers, his reactions to the infection may be stimulated sufficiently to knock out the infection altogether, in which case he will not suffer from the secondary dermal lesions; on the other hand, if he has a less severe infection, his resistance will not be stimulated to such an extent, the bartonellæ which are taken up by the reticulo-endothelial cells in the skin and/or subcutaneous tissue will later multiply, and these will give rise to secondary lesions.

The initial attack may thus be (a) severe and fatal, (b) moderately severe, (c) mild or (d) asymptomatic. The secondary lesions will follow in (b), (c) and (d), probably in an ascending order of frequency.

Recently, Tyzzer and Weinman (1939) have divided bartonellæ into two genera, *Bartonella* and *Hæmobartonella*; both are found in the blood,

but the former produces nodular lesions in animals, whereas the latter remains in the blood and produces anæmia, but not skin lesions.

If this applies in the case of bartonella infection of man, another explanation for the variations in symptomatology can be given, namely, that each infection may vary in the genera represented, and that one or more strains of each genus are usually present.

The febrile attack.—The incubation period is usually considered to be about three weeks.

There is no dramatic onset but the symptoms develop rapidly with malaise, irregular intermittent fever usually rising to between 100° and 102°F., vomiting, hiccough and progressive anæmia. There is headache, pains in the joints and bones, and great tenderness of the bones, particularly those in which there is active marrow, the sternum, ribs, etc.; this suggests some association with the observed hyperplasia of the marrow.

Most of the other symptoms are the result of the rapidly developing anæmia and need not be detailed here. Hæmorrhages into the skin and from mucous membranes, and diarrhœa are common terminal symptoms.

The course of the disease is very rapid, and profound anæmia, with red cells as low as 1,000,000 per c.mm., may be produced within a week or even less; death usually results in two or three weeks, but may be postponed for several weeks. On the other hand, after a week or so the temperature may subside completely, the acute symptoms disappear, rapid regeneration of blood may take place, and the patient may recover completely; in such cases the verruga eruptions may or may not follow within a few weeks.

The mild and asymptomatic types.—In the milder type, there are malaise, headaches, pains in the bones and joints, possibly gastro-intestinal disturbances, and an intermittent fever. The fever usually subsides a few days before the appearance of the eruptions, which may be postponed as long as sixty days.

The disease always runs a milder course in children and in them it may be symptomless; it is probably this fact that accounts for the comparative immunity of the local population in endemic areas.

Persons with bartonellæ in their peripheral blood may show no symptoms whatsoever. These persons may later develop verruga lesions.

The dermal lesions, or verruga peruana.—There are two types of lesion, (i) the miliary granulo-angiomatous eruption, and (ii) subcutaneous nodule.

The 'miliary' lesions start as small-sessile papules, usually on the sites of petechial spots, and increase in size up to that of a split pea, becoming almost pedunculated in some cases; they appear in crops so that there will be lesions of all sizes present at one time. In colour, the lesions vary from a dull pink up to a bright red, the latter in a few cases in which development has been exceptionally rapid. In consistency, they are at first shotty, but in time they become softer, and when they are retrogressing they become wrinkled. They occur in almost any part of the skin surface, but they are particularly prevalent on the extensor surfaces of the arms and legs, and on the face and neck, less frequently on the trunk and genitals, and very seldom on the palms and soles. They may be scanty, or very numerous so that in places they may coalesce.

When they are developing they cause a pricking sensation. They are not actively painful, but are easily damaged and are inclined to bleed, so that they will often have black scales of dried blood over them. When they shrink they may become very irritating.

The eruption may last for four or even six months, and a few cases have been reported in which they lasted as long as two years. When they disappear they leave no mark.

The nodular lesions have very much the same consistency as the papules but usually they are softer. They may grow to the size of a pigeon's egg. The commonest sites are on the extensor surfaces of the extremities. The skin is stretched over the nodule; this may be normal in colour, but, if taut, it usually has a pinkish colour.

When this nodule is on or near the knee, or on some other place where it is likely to be damaged, it may ulcerate and form what is known as a 'mular' lesion (apparently for the rather naive reason that mules suffer from a similar lesion); the mular lesion is a nodule with a fungating cap, like the crater of a volcano, and it is very liable to secondary hæmorrhage.

Diagnosis.—This presents few difficulties even from a clinical point of view, and is easily confirmed by finding the bartonella infection in the red cells in the febrile stage, or in the reticulo-endothelial cells of the dermal lesions. In the latter, parasites are always present, but are not abundant. Escomel (1938) advocates cultural methods as being more certain.

Treatment.—There is no specific treatment that has any established reputation. An arsenic-antimony preparation, Bayer 386B, is apparently effective in the treatment of rats infected with bartonella; in these animals, it is given in doses of 0.2 mg. per kilo. It is said to have been used with success in 14 cases of the disease in man.

Treatment in the past has mainly been aimed at maintaining the patient's strength, and providing all the necessary materials for blood regeneration. From the nature of the blood picture and from the fact that there is no actual loss of hæmoglobin outside the body, liver extract will obviously be more valuable than iron for this purpose.

Prevention.—In the absence of exact knowledge of the ætiology, no general preventive measures have been adopted in the endemic areas. From a personal point of view, the first important measure of prevention is to avoid spending a night in a known endemic area. If this is not possible then, since the disease is almost certainly transmitted by a biting insect, protection at night by a sand-fly net must be provided.

Prognosis.—Inhabitants of infected villages seem to acquire an immunity, but probably many die in childhood from the infection.

In foreign visitors to such a village, infection appears to be almost certain, and the death rate amongst those infected is of the order of 50 per cent.

REFERENCES

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|--|----|----|--|
| BARTON, A. L. (1909) | .. | .. | <i>Cron. Med. Lima</i> , 26 , 7. |
| ESCOMEL, E. (1938) | .. | .. | La Maladie de Carrion ou Verruga du Pérou les Dernières Acquisitions. <i>Bull. Soc. Path. Exot.</i> , 31 , 536. |
| MAYER, M., BORCHARDT, W., and KIKUTH, W. (1927). | | | Die durch Milzexstirpation auslösbare infektiöse Rattenanämie. <i>Beihefte, Arch. Schiffsu. Trop.-Hyg.</i> , 31 , 291. |
| STRONG, R. P. et al. (1915) | .. | .. | <i>Rep. First Expedition, South America</i> , 1913. Harvard University Press, Cambridge, Mass. |
| TYZZER, E. E., and WEINMAN, D. (1939). | | | <i>Hæmobartonella</i> , N. G. (<i>Bartonella Olimi</i> Parte), <i>H. Microti</i> , N. Sp. of the Field Vole, <i>Microtus Pennsylvanicus</i> . <i>Amer. J. Hyg.</i> , 30 , 141. |

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Definition.—Yellow fever is an acute specific fever of varying severity, but characteristically one of great intensity and associated with toxic jaundice and albuminuria; it has a limited tropical distribution, and is caused by a filtrable virus, which in the urban, either epidemic or endemic, form of the disease is transmitted from man to man by *aedes* mosquitoes, and in its jungle form is transmitted from its jungle reservoir to man by other means.

Introduction.—The importance of yellow fever to India and countries further east lies in the fact that, though the disease has up to the present never appeared in these countries, there seems to be no explainable reason why it should not invade them at some, near or distant, future date. The history of this disease shows that it is capable of geographical extension, and, in the American continent, from time to time it has invaded countries which were previously free from it. In India, the stage is apparently set for an explosive epidemic should the virus ever be let loose here. It is therefore essential that we in this country should take every precaution to prevent this catastrophe and, if this invasion ever occurs, we should be ready to deal promptly with any isolated case that appears, in order that we may stamp out the disease before it gets a firm footing.

In this matter, India has not only herself to consider, but she has a special mission in being in the front line in the defence of the rest of Asia; she has not only her hundreds of millions of inhabitants to protect, but the thousand million or so in China and the Far East, for, if yellow fever were to gain an effective hold in this country, it is almost inevitable that it would sweep through the rest of tropical Asia, and in these sanitarily backward countries there would be little hope of controlling it until it had run its course and decimated the populations of this and other eastern tropical countries.

Whilst yellow fever is a disease that has from time to time extended its domain, it is, on the other hand, one that has been very effectively controlled in many countries where it was firmly established and had become a serious menace to the community. Yellow fever has always been held up as an example of how, medical research having shown the way, sanitary organization has put into effect measures that have been brilliantly successful; these measures were so successful that at one time the hope was cherished that eventually man might completely triumph over this disease and finally banish it from the world. However, recent investigations have brought to light facts which show that this hope is vain. The discovery of the 'jungle' form of yellow fever, the virus of which, if not identical with that of the classical urban yellow fever, is capable of urbanization, has shown that there is a reservoir of yellow fever which may be limitless and over which man may never be able to exercise effective control.

Figure 86 shows graphically the data upon which these hopes were founded and then shattered.

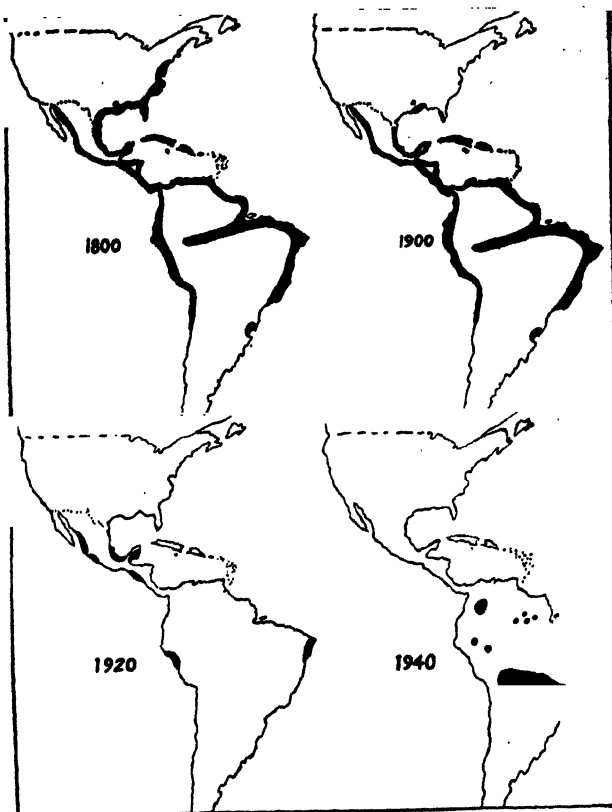
problematical safeguards.—It was at one time suggested that there be minor differences in the *aedes* mosquitoes of this country, which make them incapable of transmitting yellow fever; this has been shown not to be the case, for *aedes* collected in India have been used in transmission experiments and have been shown to be capable of transmitting the infection.

Figure 86 demonstrating three phases in the history of yellow fever in the American continent.

Phase 1.—Between 1800 and 1900 the disease almost entirely disappeared from the United States, largely as a result of general sanitary improvement.

Phase 2.—The complete disappearance from the United States and the reduction in Central and South America between 1900 and 1920 was due to the application of the knowledge that the mosquito *Aedes ægypti* was the main transmitter, and to measures directed against this insect.

Phase 3.—The apparent extension of the disease between 1920 and 1940 is really an extension of our knowledge of the disease, with the discovery of jungle yellow fever.



A second hope, namely, that dengue, or some other similar widespread infection, might have produced immunity to yellow fever in our populations, has also been abandoned after the discovery that, of the many hundreds of samples of blood collected in various parts of India, none showed any evidence of immune bodies.

We are thus thrown back on the vague hope that, as yellow fever has not appeared hitherto, there must be an unknown factor, some special local condition, which prevents its gaining a footing.

It is not necessary to introduce this 'unknown factor', for the explanation may be that the virus has never arrived in this country, either in an infected individual or in a transmitting mosquito, but, because this has not happened in the past there is unfortunately no guarantee that it will not happen now or at some future date. This danger is vastly increased by the enhanced speed of transport generally, and particularly by the increase in aerial communications between the yellow-fever areas and the rest of the world. The only safeguard then is increased watchfulness to prevent either an infectious patient or an infected mosquito from arriving in this country; the measures that are in operation to effect this will be described below.

Historical.—There is evidence that the disease has existed on the American continent from the time of Columbus; a serious epidemic is reported as early as 1493 in San Domingo. There are many early references to a disease that was undoubtedly yellow fever, from this date onwards, and in the eighteenth century it was so well known that quarantine regulations were introduced in connection with it. It was endemic over a much wider area in earlier days, but it had disappeared from many old endemic areas, even before the exact mode of transmission was known,

presumably as a result of the introduction of general sanitary measures. In America, epidemics were reported as far north as New York and Philadelphia, but during the last fifty years only one epidemic of any importance, the epidemic in New Orleans in 1905, has occurred in the United States. In its eastern sphere, it was at one time apparently rife in Spain, including Gibraltar, in the Canary Islands, and all along the west African coast. The disease played an important part in naval and military history: in the sixteenth century Drake's fleet was badly infected after calling at West Coast and Spanish ports, and in 1800 a Napoleonic army that landed in the West Indies was almost completely destroyed by yellow fever.

In 1881, Carlos Finlay, a Cuban of Anglo-French parentage, suggested that the disease might be transmitted from man to man by mosquitoes, and carried out experiments to demonstrate this. However, this means of transmission was not generally accepted until, Ross' work on malaria having led to a reconsideration of Finlay's theory, the historical experiments were carried out in 1900 by the American yellow-fever commission consisting of Walter Reed, James Carroll, Jesse Lazear, and Aristides Agramonte. They demonstrated the *aedes* transmission, and further showed that yellow fever was not transmitted by contact or other means. Lazear died of yellow fever, and Carroll developed yellow fever after being bitten by an infected mosquito in an experiment, but recovered. As a result of these observations, control measures were instituted against *aedes* mosquitoes in Central and South America, and by 1920 the incidence of the disease had been reduced almost to vanishing point (*vide* figure 86).

Aedes aegypti was first the only mosquito incriminated; later, other *aedes* were shown to be potential transmitters; then followed the discovery of 'jungle' yellow fever, with its tremendous implications: jungle mosquitoes, notably *Hamogogus capricorni*, were incriminated as transmitters, with some jungle animal, possibly monkeys, as the reservoir of the virus.

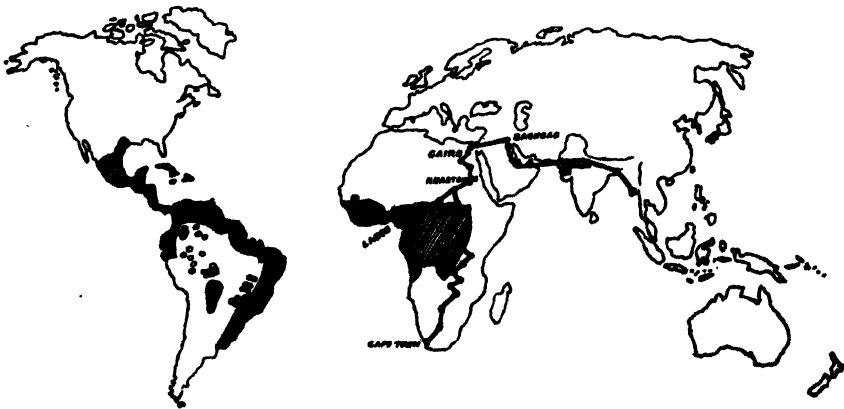


Figure 87: Distribution of yellow fever. The endemic areas of urban yellow fever at the present day are shown in black; potential areas are shaded; and the known distribution of jungle yellow fever is shown by small circles. The air routes to India are shown by a heavy black line.

EPIDEMIOLOGY

Geographical distribution.—Yellow fever is now confined almost entirely to the tropics. Most of the endemic areas are on the Atlantic sea-board, though in South and Central America some parts of the Pacific coast are included, and in Africa the endemic areas extend from the west coast for some thousands of miles inland.

In the American continent, the coastal areas from Mexico in the north, throughout the countries of central and down the east coast of South America almost as far as Buenos Aires, all the islands of the West Indies, and the west coast as far south as Ecuador, are all endemic areas, and recently a few foci have been found in Bolivia.

In Africa, it occurs on the west coast from latitude 15°N. to 10°S., from Senegal down to Angola, and inland as far east as the Anglo-Egyptian Sudan, Uganda, and Tanganyika and even into Abyssinia. An epidemic in the Nuba Mountains in the Sudan, which has been recognized as a 'silent area' for some years, has recently occurred (*vide infra*).

There are no endemic areas on the east coast of Africa, nor anywhere in Asia.

Epidemic features.—From an epidemiological point of view, there are two forms of the disease, the urban and the jungle. The urban form is usually endemic, but it may be epidemic especially when new territory is invaded. The jungle form is usually sporadic, but may also become epidemic.

It is suggested that, in its original form, yellow fever was a disease of some jungle animal, that it was transmitted to man sporadically by jungle mosquitoes, and that it was then conveyed by man to the towns where, transmitted by *aedes* mosquitoes, it becomes at first epidemic and then endemic.

The epidemiology of the disease has recently been studied in two ways, by viscerotome surveys, and by the mouse-protection test (*see p. 299*).

The viscerotome is an instrument which has been designed for removing pieces of liver without a full post-mortem examination; in all cases of death through an uncertain cause, a specimen is taken and examined microscopically (*vide infra*). The mouse-protection test is a test to show the presence of protective antibodies in the blood, and a positive result indicates that the patient has at some time suffered from yellow fever. These two methods have shown the existence of the disease in many parts of South America and Africa where its presence was hitherto not suspected, and the findings have usually been confirmed later by the discovery of clinical cases. In Africa, in certain areas in the Sudan for example, many 'protected' individuals have been discovered, though the disease has never been reported. These have been called 'silent' areas, and, recently, in one such area in the Anglo-Egyptian Sudan, *i.e.* in the Nuba Mountains near Malakal, the 'silence' has been broken by an explosive epidemic. In known endemic areas where the disease has not appeared in epidemic form for many years, children born after the last epidemic have not shown positive protection tests, whereas older children in the same area have provided a large percentage of positives, and, finally, in Asia and places distant from the yellow-fever areas, no evidence of antibodies has been found in the blood of the inhabitants.

Season and altitude.—High temperatures, 75°F. and above, and high humidity favour the spread of the disease. It is therefore confined mainly to coastal areas in the true tropics, and its highest peak of incidence is in the hot damp months of the year. It seldom occurs much above sea level, though it has been reported from Sao Paulo (2,500 feet).

Both sexes are equally susceptible, but the disease appears to occur more frequently in men; this applies in particular to the 'jungle' form of the disease which is almost entirely confined to forest workers. Persons of all ages are attacked, but in children the disease takes a milder form, and in old people and in alcoholics it is particularly fatal. All races seem equally susceptible but the disease is usually more severe in foreigners in endemic areas than in the indigenous inhabitants (*vide supra*).

ÆTIOLOGY

Historical.—Many organisms have been isolated from patients and presented as the cause of yellow fever, but the classical mistake of Noguchi is the only one worth recording, as Professor Noguchi was a brilliant worker who was led down the wrong path by a clinical mistake—not his own, for he was not a doctor. He isolated a leptospira from cases presented to him as yellow fever, and named it *Leptospira icteroides*. It was in fact *Leptospira ictero-hæmorrhagiae*, the causal organism of Weil's disease, which was the disease that these patients were really suffering from. Noguchi died of yellow fever whilst carrying out experiments in West Africa where, dealing now with true yellow fever, he had entirely failed to confirm his earlier findings—a tragic sequel to perhaps the first mistake of a brilliant investigator.

Meanwhile, Adrian Stokes (who later died of yellow fever), Bauer, and Hudson infected Indian monkeys with yellow fever by means of blood filtrates of patients, and thus proved that the disease was caused by a filtrable virus; they further demonstrated that very small quantities of the serum of yellow-fever convalescents protected a monkey.

The virus.—This is a filtrable virus, of the size of about 18 to 27 micro-microns ($\mu\mu$): it is killed at 60° to 65°C., but survives freezing *in vacuo* for many years. It also withstands the action of some strong disinfectants, such as phenol 1 in 150 at 30°C., but is inactivated by the photodynamic action of methylene blue—1 in 100,000. Like other filtrable viruses, it will not multiply except on living tissues.

Tropism.—The virus may be, (i) viscerotropic (or pantropic)—as in the patient with yellow fever or in animals inoculated subcutaneously or intra-viscerally from such a patient, (ii) neurotropic—after serial inoculation in mouse brain, or (iii) atropic, i.e. free from any organotropism—after serial cultivation on nerve-free chorio-allantoic membrane. There is some evidence that the neurotropic virus may possibly revert to the viscerotropic phase under certain conditions, but there is no evidence that egg-grown virus can re-acquire its viscerotropic or neurotropic tendency.

Susceptible animals.—The rhesus monkey and the mouse are most susceptible to infection. *Silenus rhesus*, the common monkey of the Indian plains, is probably the most susceptible animal after man, but other Asiatic, African and South American monkeys and apes are susceptible, and certain species of these may form the reservoir of the jungle form of yellow fever (*vide infra*).

The European hedge-hog also is susceptible to the virus.

Transmission.—Infection is very easily acquired in the laboratory, and many workers have become infected by contact with the blood of a patient or with infectious morbid material from experimental animals; before the introduction of prophylactic inoculation, nearly every member of the staff of the Rockefeller Foundation yellow-fever laboratory developed yellow fever.

The mosquito *Aedes ægypti* is the important transmitter of the urban form of yellow fever from man to man; other mosquitoes have been shown to transmit it under laboratory conditions, e.g. *Aedes luteocephalus*, *stokesi*, *vittatus*, *africanus*, and *simpsoni*; *Culex thalassus* and *Mansonia africana* in Africa; *Hæmogogus capricorni*, *Aedes scapularis*, *fluviatilis*, and *leucocelæmus*, in South America; and *Aedes albopictus* in the East Indies.

The mosquito becomes infected if it 'bites' a patient during a period from the appearance of the first symptoms (and probably even earlier, as in the monkey the virus can be demonstrated within 12 hours of inoculation) up to the end of the third, possibly the fourth, day of the disease; the virus infection develops in the mosquito for some days before the latter becomes infectious, the time varying between four and twenty-eight days according to the temperature at which the mosquito is kept; under natural conditions in the endemic areas, the average latent period is about twelve

days, and from this time onwards and for the rest of its life the mosquito may be infectious; the infection is transmitted by the 'bite'.

The method of transmission of 'jungle' yellow fever has not been established. Certain jungle species of mosquitoes, *e.g.* *Hæmagogus capricorni* that live and breed in tall jungle tree-tops, and *Aedes simpsoni*, have been found infected in nature, and shown to be potential transmitters. In this form of the disease, transmission to man is probably an accident in an epizootic cycle, the disease being normally transmitted from animal to animal by the same, or some other, insect vector; as the animal reservoir, monkeys are suspected, because in jungles where the disease occurs sporadically, monkeys have been shown to carry antibodies in their blood.

Factors determining incidence.—The incidence of the disease is conditioned by (a) the number of the vector mosquitoes, (b) the supply of the virus, and (c) the extent of the susceptible material.

Aedes is a domestic mosquito and thrives best in towns. In the urban form, man is the only source of infection, and it is probably mild and unrecognized cases of the disease that are the most important source of the virus. The highest concentrations of (a) the transmitter, (b) the source of infection, and (c) susceptible individuals are found in towns, and it is therefore here that the epidemics usually occur.

Immunity.—There is no natural immunity to this infection. Populations in endemic areas subjected to frequent infection appear to acquire a degree of immunity, for the death rate amongst indigenous inhabitants is very much lower than amongst foreigners.

One attack confers complete immunity—no authentic second attack has ever been reported, and antibodies have been demonstrated in an individual 75 years after the disease. The immunity of natives is due to infection in earlier life, when the symptoms may be overlooked. The presence of immune bodies in the blood can be measured by the mouse-protection test (*vide infra*); the test is of little value as an individual diagnostic measure, but is an invaluable procedure for obtaining retrospective information regarding the past history of a population, *vis-à-vis* yellow fever.

Immunity can be conferred by vaccination; such immunity is effective about ten days after the inoculation, and lasts for at least two years.

Mouse-protection test.—When a population is to be tested, at least 25 adults and 25 children should be chosen at random. Ten to fifteen c.cm. of blood is taken from each, and the serum separated. Three c.cm. of the serum to be tested is mixed with 1.5 c.cm. of a 20 per cent emulsion of the brain of a mouse infected with the neurotropic virus. Of this mixture, 0.6 c.cm. is then injected intraperitoneally into six mice which have previously had an intracerebral injection of 0.03 c.cm. of 2 per cent sterile starch solution.

Observe for 10 days; if more than three survive, the test is positive, but if four or more die it is negative, that is, no immune bodies are present.

By diluting the serum further, an exact quantitative test is possible which can be used to demonstrate a rising titre for diagnostic purposes.

An intermediate result, that is one in which three survive and three die, is a doubtful result, and the test should be repeated. This will necessitate the use of more serum and for this reason some workers advocate taking a larger quantity of blood in the first instance.

PATHOLOGY

Morbid anatomy.—The typical post-mortem picture includes the olive discoloration of the skin (in the fair-skinned races) and of all the organs and tissues, ecchymoses all over the body, especially at pressure points, petechial hæmorrhages in the mucous membranes, sometimes extensive hæmorrhages into the stomach, muscles, and other tissues, a yellow nutmeg liver, fatty degeneration of the heart, petechial hæmorrhages in the brain, and occasionally extensive hæmorrhages into the ventricles.

Histological examination of sections of the liver shows characteristic changes that are usually far more extensive than the gross appearance of the organ suggests. The parenchyma cells of the liver undergo a progressive degeneration. These changes are essentially non-inflammatory; the main ones are cloudy swelling, fatty degeneration, and a characteristic hyaline necrosis of the liver parenchyma cells, without interstitial changes.

One of the earliest changes is a finely granular appearance of the cytoplasm with some oedema, so that the hexagonal shape of the liver cells is lost. The fatty changes are the most constant, and are a *sine qua non* in yellow fever; in the early stages there are fine droplets of fat which coalesce so that, as the degeneration progresses, large droplets appear. The fatty changes appear to be complementary to the necrosis, being more apparent in the non-necrotic portions of the liver.

The cytoplasm undergoes coagulative necrosis; it may become vacuolated, and hyaline eosin-staining areas appear; chromatolysis occurs in the nuclei, which are usually rounder and smaller than normal; there is at first margination of the chromatin material, and then red acidophil bodies appear; Küpffer's cells show hyperplasia, increasing in size and number.

Starting in the mid-zonal areas, there is eventually complete disorganization of the normal histological picture of the liver. The full range of changes will not be found in all cases, but the most characteristic finding is the 'Councilman cell', which is a parenchyma cell, now globular in shape, in which the full range of hyaline necrotic changes has taken place; the nucleus has undergone chromatolysis, and the cytoplasm contains 'punched out' hyaline acidophil bodies.

In cases in which death is unusually delayed—that is, beyond the tenth day—the Councilman cells undergo a further degenerative change, and ochre bodies appear.

The extent of the parenchyma involvement will vary from 5 to 95 per cent; in the latter case, only a few areas around the portal sheaths at the periphery of the lobule and around the central vein remain intact, and even these usually show some cloudy swelling under such conditions.

These changes account for the toxic jaundice and hæmorrhages.

In the kidneys, there is cloudy swelling and fatty degeneration, more apparent in the convoluted tubules than in the glomeruli; there are hæmorrhages into Bowman's capsule and in the cortex, and the tubules are blocked with epithelial debris. These changes readily explain the albuminuria and the eventual anuria.

The spleen shows few macroscopical changes, but microscopically there is evidence of endothelial proliferation at the expense of the lymphoid tissue.

In the heart, granular and fatty changes of the myocardial musculature are constant in fatal cases, and hyaline degeneration is found in a few cases; the low blood pressure and pulse rate, and the venous congestion that appear in the second, toxæmic stage, can be accounted for by these changes.

The liver changes are the most constant and characteristic, but in some cases one of the other vital organs, the kidney and the heart, will appear to bear the brunt of the attack.

The pathology in the jungle form of yellow fever is apparently identical with that of the classical form.

Blood picture and blood chemistry.—There is a leucopenia during the early stages up to the fifth or sixth day, after which there may be a slight leucocytosis. During the first few days there is a lymphopenia which gives place to a granulopenia: later, there is a relative increase of large mononuclears.

Very early there will be an increase in hæmobilirubinæmia (*indirect van den Bergh test positive*), and later, when jaundice develops, bili-

rubinæmia (*direct van den Bergh test positive*); there is a lowered fibrinogen content, and consequently increased clotting time, and hypoglycæmia. All these findings indicate gross liver dysfunction. There is also an increase of guanidine in the blood, a condition which in animals has been shown to be associated with the occurrence of hæmorrhages.

Urine.—A cloud of albumin may appear in the urine early; but by the third or fourth day there is usually a very heavy cloud, amounting to 0.3 to 0.4 per cent in severe cases. With the development of jaundice, bile will appear, and in severe cases there will be hæmaturia. The urine is often scanty, and the urea and uric acid excretion may be low.

SYMPTOMATOLOGY

Clinical types.—All degrees of severity will be encountered and division into types is artificial but will perhaps facilitate description.

(i) *The abortive attack.*—There is a mild febrile attack, lasting from a few hours up to a day in which there is malaise and headache; this type of attack may be mistaken for a mild influenza, but the disproportionate severity, the presence of albumin in the urine, and the slowing of the pulse in convalescence should raise suspicion as to its true nature.

During an epidemic, *e.g.* the Nuba Mountains outbreak, there is often evidence that about 70 per cent of the attacks are apparently sub-clinical, but it is probable that, if those natives who showed a positive mouse-protection test could have been observed closely, the majority would have shown a mild febrile attack of this kind.

(ii) *Incomplete attack.*—There is a sharp rise of temperature, with severe headaches, pains in the body and possibly vomiting; the temperature shows the usual fall on the third day and may even rise again; the pulse is characteristically slow, but there is no jaundice nor any of the other severe symptoms. However, in such cases, a considerable degree of albuminuria with cylindrical casts may develop from the third to the fifth day.

(iii) *The classical attack.*—This is described below in more detail.

Incubation period.—This is usually from three to six days in the natural infection, but, in the case of laboratory infection, instances where the interval was as long as twelve days have been reported.

The onset.—In the typical severe case of yellow fever, the onset is sudden, with fever and possibly rigor, and a rapid, full and bounding pulse, very severe frontal headache with pains in the eyeballs, and photophobia, pains all over the body but particularly in the loins and bones, an intense burning sensation and dryness of the skin, a furred sharp-pointed tongue with a pink tip and edges, a red and swollen face with the eyes bloodshot and 'beady', anorexia, and severe prostration.

The course of the disease.—As the infection subsides, this febrile congestive stage may be followed by a short interlude when the temperature is normal or sub-normal and the pulse rate drops, but this 'period of calm' is rapidly succeeded by a stage of intense toxæmia; the blood pressure falls, and, though the temperature usually rises again, the pulse rate remains low. The toxæmia increases, there is nausea and vomiting, jaundice appears and increases, there are hæmorrhages from mucous membranes, into serous cavities, and subcutaneously, especially into the scrotum and vulva and at pressure points, and eventually there may be anuria.

In fulminant cases the early febrile stage will merge into the toxæmic stages without the characteristic interlude.

Termination.—Death may occur in the febrile stage from hyperpyrexia with delirium, or in the 'period of calm' and be associated with profuse hæmorrhages from all mucous membranes, with black vomit, melæna and hæmaturia, the patient passing into a comatose state. Death seldom occurs

before the third day or after the eleventh, and if the temperature is down by the seventh day the prognosis is good.

The fever.—The temperature rises sharply, reaching 103°F. or higher in 24 hours and remains high for three or four days; it then falls, usually rather rapidly and may become sub-normal for 24 hours—the 'period of calm', but it may rise again to 101° or 102°F. for another two or three days or more (see charts, figure 88).

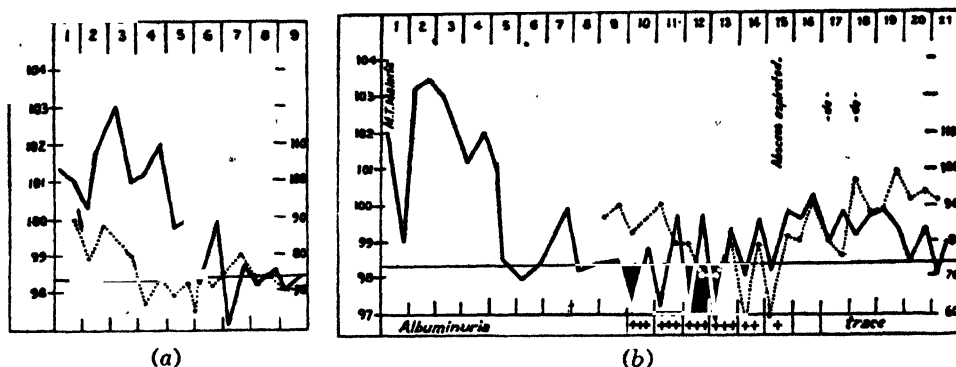


Figure 88 : Two yellow-fever temperature and pulse charts :

(a) A relatively mild case.

(b) A case complicated with malaria and abscess formation (Kirk *et al.*, 1941).

The pulse.—This is rapid, full and bounding at first, but the pulse rate tends to fall before the temperature; it may drop to 50 per minute or even lower during the 'period of calm', and it seldom rises beyond the normal level during the second febrile period. A steady pulse with a rising temperature, or a falling pulse with a constant temperature constitutes Faget's sign, which is a point of diagnostic importance.

Jaundice appears on the third or fourth day and is progressive—up to a dark-brown colour in severe cases. Its earlier appearance suggests a bad prognosis. It is a common but not a constant sign, and even in moderately severe cases it may not be prominent. It is naturally associated in severe cases with bile in the urine and a bi-phasic van den Bergh reaction.

Petechial hæmorrhages may appear, and a characteristic erythema of the scrotum or vulva is common. In severe cases large purpuric patches appear.

Other symptoms.—Insomnia and restlessness are common, but delirium is rare except as a terminal condition. Vomiting may occur with the onset of the fever, as with any high fever, but the characteristic severe vomiting occurs from the third day onwards and may assume a coffee-ground character, the typical 'black vomit' of yellow fever, which always portends a grave issue.

DIAGNOSIS

A. The clinical diagnosis.—The clinical diagnosis of a typical case presents little difficulty. The sequence of events is very characteristic; there are two distinct stages in the attack, the early febrile congestive stage and the subsequent intense toxæmia with a falling blood pressure, a disproportionately slow pulse, increasing jaundice, and possibly hæmorrhages. The early appearance in the urine of albumin, which increases rapidly in amount until anuria supervenes, will almost make the picture diagnostic.

Even if jaundice is slight during the course of the disease, it will in every fatal case be marked at the time of death.

During the presence of a recognized outbreak, the occurrence of mild fever of two or three days' duration associated with a disproportionate degree of headache and the presence of albuminuria will lead to a suspicion

of yellow fever. In an isolated case of the mild type, it will be almost impossible to make a clinical diagnosis.

B. Laboratory diagnosis. Tests for the presence of yellow-fever virus.—The rhesus monkey is a susceptible animal, and can be infected by the blood taken from a patient during the first three days of the disease; the monkey will die of acute yellow fever within a few days.

Similarly, intracerebral inoculation into mice will cause an encephalitis, within seven to fourteen days, but, as other virus infections also cause an encephalitis, it is essential that such tests should be controlled by protection tests with known immune (yellow fever) serum. Blood taken for such tests will not retain its virulence even in the ice-chest more than a few hours, but it will in the frozen and dry state. It is therefore important to take the blood at the earliest possible date in a case of suspected yellow fever, and either to carry out the tests immediately, or to freeze and dry the material until the test can be done; in the latter case, the results will be less certain.

Tests for the presence of immune bodies.—When, in the later stages of the infection, antibodies develop, their presence can be demonstrated by the mouse-protection test; if the patient's serum, after being mixed with the virus and injected into a mouse, protects that mouse from the effects of the injected virus, this is presumptive evidence that the patient has at some time or other suffered from yellow fever. Although these antibodies appear in the blood at an early date and neutralize the virus in the patient's blood, so that mosquitoes are not usually infected after the third day of the disease, for purposes of the mouse-protection test the antibodies are seldom present in sufficient quantity to ensure a positive result before about the twenty-first day; the diagnostic value of this test is thus limited. (For technique see p. 299.)

The test with the neurotropic virus cannot be carried out in India as the importation of neurotropic or pantropic virus is forbidden by law. The value of an intracerebral test in white mice in which the 17D virus (the vaccine virus) is used is under study, and this may be found applicable in India and other eastern countries which are at present free from yellow fever.

C. Post-mortem diagnosis.—The characteristic changes in the liver enable a post-mortem diagnosis to be made by naked-eye and histological examination.

Portions of the liver can be taken for the purpose by carrying out a full post-mortem examination or, when this is not permitted, by removing a piece by means of the viscerotome, the instrument devised for removing small pieces of tissue without opening the abdomen. The tissue removed is placed in Zenker's fluid and histological sections are cut. The histological picture in yellow fever is characteristic (see p. 300).

Viscerotomy.—The viscerotome is, essentially, a long metal box with one end closed and the other consisting of four cutting blades, one of which is flexible and movable (figure 89). When the instrument is thrust into

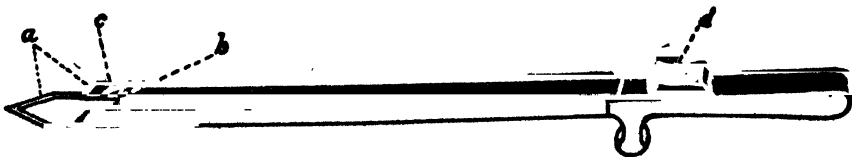


Figure 89 : The viscerotome.

- a. Cutting edges for introducing viscerotome.
- b. Sliding guillotine blade.
- c. Groove for sliding guillotine blade.
- d. Thumb grip for closing the sliding guillotine blade.

a solid organ, the three fixed blades make a deep U-shaped incision; the flexible blade is moved forward, completes the open side of the U to make a more-or-less square incision and then, dipping downwards behind the rectangular block of tissue to meet the lower blade, it severs a piece from the rest of the organ and encloses it in the viscerotome; the instrument is then withdrawn, opened, and the contained piece of organ removed.

Technique.—The entry point of choice is in the epigastrium, just below the ensiform cartilage and close to the costal margin on the right side. The direction of the thrust is at an angle of about 10° with the horizontal and about 20° with the body surfaces, from left to right (figure 90). The instrument which must be closed (figure 91a) is pushed through the skin and the abdominal wall with a sharp thrust. When the lower fixed blade has penetrated the liver, the flexible blade is opened about an inch; the instrument is thrust further into the organ for about half an inch, and then the flexible blade is pushed forward again and held firmly in this position while the viscerotome is withdrawn from the body.

The flexible blade is withdrawn and the piece of liver removed and placed in solution for subsequent sectioning.

The hole made by the instrument is now plugged with cotton-wool to prevent oozing, and the skin wound is sewn up if this is considered necessary. The warning may seem superfluous, but it must be emphasized that this viscerotomy is only a *post-mortem procedure*.

Differential diagnosis.—The most constant and prominent symptoms of yellow fever are fever and jaundice; therefore the diseases with which it is most likely to be confused are severe malaria of the 'bilious remittent' type, blackwater fever, Weil's disease, infective hepatitis, and catarrhal jaundice. Certain fatal liver conditions, such as acute yellow atrophy and carbon tetrachloride poisoning, might be mistaken for yellow fever; in the latter the hepatic necrosis is central. The milder forms of yellow fever might be confused with relapsing fever, dengue, or influenza.

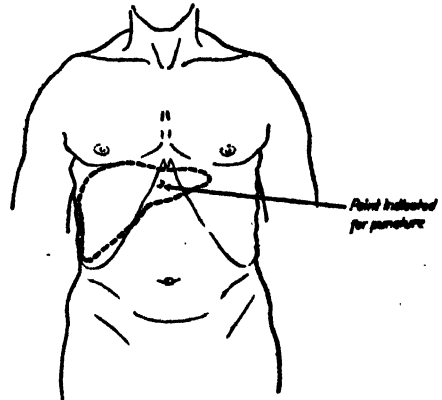


Figure 90: Showing point of entry and direction of thrust of the viscerotome.



Figure 91: Viscerotome (a) shut and (b) open.

In the malarial fevers the parasite (a) should be easy to demonstrate, while the jaundice appears earlier and tends to improve; in blackwater fever parasites may not be found, but the hæmoglobinuria of this condition should not be mistaken for the hæmaturia of yellow fever. Similarly, in relapsing fever the spirochæte is usually found in the peripheral blood. The saddle-back temperature of dengue is not unlike that of

yellow fever, but the dengue rash when present is characteristic, and jaundice does not occur.

The only real difficulty that is likely to arise is in differentiating Weil's disease, and in this case we have the precedent of Noguchi's classical mistake. (For the exclusion of Weil's disease see p. 251.)

Precautions.—If there seems to be a serious possibility that the case is yellow fever, the utmost precautions must be taken immediately and the patient kept rigidly under a mosquito net day and night. Also it should be remembered that the virus is present in the patient's blood and is

unneutralized by antibodies for at least three and in some cases up to four days, and that therefore every care should be taken to prevent his blood touching anyone's unprotected skin during the process of blood withdrawal. (In most countries immediate notification to the health authorities is imperative.)

PREVENTION

For the disease to be spread, there are three requirements—the virus, the transmitting mosquito, and the susceptible population.

The main successes in yellow fever prevention in the endemic areas have been achieved by *aedes* control. *Aedes* is a mosquito which is very local in its habits; it bites during the day, so that thorough spraying of offices, and other living rooms, as well as bedrooms, is necessary. It breeds in small local collections of water, in old tins, broken utensils, anti-formicas, hollow tree trunks, etc., and is therefore easily controlled by general sanitary and water tidiness. In dock areas the fresh-water supplies of small country boats is often a source of breeding, and receptacles in which the water is stored must be kept covered. Where one is dealing with an undisciplined population, very careful inspection at frequent but irregular intervals is essential. It has been found that, provided the *aedes* index is reported below 2 per cent (that is, only 2 per cent of houses inspected show *aedes* breeding places), yellow fever will not spread.

Aedes seldom flies more than a few hundred yards from its breeding place, and therefore control for an area of four hundred yards around a house, or aerodrome, is usually considered sufficient. Similarly, if ships are moored a quarter of a mile from the shore in a yellow-fever port, they are considered to be safe, but this does not take into account the danger of mosquitoes being brought from the shore in small visiting craft, or in coal or other lighters.

It is beyond the scope of this book to describe in any detail the procedures that should be adopted against these mosquitoes, but besides the elimination of breeding places and other anti-larval measures and the destruction of the adult mosquitoes by spraying (*vide* p. 115), for personal protection, some deterrent application should be smeared on the ankles, wrists, neck and other exposed parts of the body. For this purpose the following makes an effective cream (*see* also p. 119):—

Citronella oil	8 parts	Soft paraffin	..	57 parts
Camphor	1 part	Hard paraffin	..	29 parts
Liquid extract of pyrethrum			5 parts			
						100 parts

Another measure that is now being adopted with increasing frequency in several countries is the reduction of the susceptibility of the population at risk by **prophylactic inoculation**.

History of yellow-fever vaccination.—Hindle in 1928 suggested prophylactic inoculation, and Sawyer *et al.* (1931) introduced sero-vaccination, which consisted in giving an emulsion of the liver of an infected monkey in combination with convalescent serum; the latter prevented the development of the disease, but allowed antibodies to develop. In 1930 Max Theiler produced a neurotropic virus, and by 1934 vaccination with neurotropic virus *plus* immune serum was a well-established method of yellow-fever control. More recently, Findlay and McCallum (1937) and others have grown the virus *in vitro* on chorio-allantoic chick membrane from which nerve tissue has been removed, and produced a virus that has lost not only its viscerotropic but also its neurotropic, whilst still retaining its antigenic, properties. With this virus, vaccinations numbering millions have now been carried out.

The vaccine is made from a strain which was originally a virulent pantropic virus that had been passaged some hundreds of times on mouse-embryo tissue-culture medium until it completely lost its viscerotropic

qualities and became a neurotropic virus: then it was passaged, again some hundreds of times, on chick embryo from which the brain and spinal cord had been removed, so that it lost its neurotropic qualities. The first virus thus made caused no serious trouble, but an appreciable percentage of those inoculated suffered from jaundice; this was possibly due to an accidental contamination with some other virus. The present strain is entirely innocuous; the injection is not followed by any local or general reaction*; only one injection of 0.5 c.cm. (1,500 mouse-protection units) is necessary, and it produces an immunity which is protective from the tenth day and lasts for a considerable time—there is some diminution in the protective power of the blood at the end of two years, and revaccination is recommended after this interval.

All persons dealing with yellow-fever patients or infected animals, their blood or excreta, or the preparation of vaccines, should be inoculated. In South America and Africa, wholesale inoculations are being carried out, especially in areas where the jungle form of yellow fever occurs, as there is no other measure of control that can, in our present state of knowledge, be used in these circumstances.

Special measures in India.—In this country, the susceptible population and the transmitting mosquitoes are abundant and relatively uncontrollable, so that the main preventive activities must be aimed in the third direction. The virus has not yet arrived in India and our first consideration must be its exclusion from this country.

Towards this end a very great deal is being done. Air traffic has introduced a new source of danger and it is on this that most attention is now being centred, though other possible channels of entry, *e.g. via* Bombay and other west-coast sea-ports where for many years precautionary measures have been in force, are not being forgotten.

We must first return to Africa. The planes from Lagos on the West Coast, after passing through active yellow-fever areas, join the Cape-to-Cairo route at Khartoum. There is a considerable amount of air traffic from Lagos to Khartoum and thence to Cairo. It is thus obvious that a person could get on board a plane at Lagos in the early stages of the incubation period of yellow fever, change at Khartoum, again at Cairo, where he could pick up the regular service plane from Europe to India, and reach Karachi even before symptoms had developed. Further, Malakal, an aerodrome in the Anglo-Egyptian Sudan on the Cape-to-Cairo route, has long been recognized as a 'silent' yellow-fever area, for a large percentage of the population have antibodies in their blood, as shown by the mouse-protection test, and from time to time suspicious cases have been reported. Such 'silent' areas are potential dangers, and from them an infected person might arrive in India at an even earlier stage. It was therefore laid down by the International Sanitary Convention for Aerial Navigation that, for purposes of this convention, 'silent areas' shall be treated as yellow-fever areas.

Notification is cabled from Khartoum to Karachi whenever a passenger from an endemic area leaves for India, so that all necessary precautions may be taken. In addition to this, no planes are allowed to come to

* Recently, an infective hepatitis has recurred amongst U.S.A. troops that had received prophylactic injections from certain batches of yellow-fever vaccine. The first symptoms appeared between 40 and 100 days after vaccination, and the resultant invalidism averaged two months. Official figures are naturally not yet available, but many thousands of soldiers were affected; deaths occurred, but the mortality was only two per thousand of hospital admissions. The cause was not the yellow-fever virus, but a contaminating virus that was introduced in human serum used in the preparation of the infected batches. The vaccine is now made without any human serum, and the accident is not likely to recur.

Karachi from the endemic or 'silent' areas unless they have passed through either Khartoum or Cairo, which are anti-amaryl aerodromes, [that is to say, especially equipped for anti-amaryl (anti-yellow-fever) measures, which include local control of *aedes* mosquitoes and 'disinsectization' of the aeroplanes before they leave], and unless they carry a certificate of disinsectization from a competent authority in one of these two places. For disinsectization 'pyroicide 20', a pyrethrum spray with a kerosene base, has been used, but there are similar preparations with watery bases, which are safer and almost, if not quite, as effective (see p. 116).

In India, the further precautions that are taken include the following :—

(a) Another thorough spraying of the inside of the plane is carried out before the passengers disembark or the luggage is removed.

(b) If the aircraft arrives without a 'disinsectization' certificate, it will be 'disinsectized' on arrival in India and all persons on board, other than those who have been protected against the disease by a previous attack or by satisfactory inoculation, will be subjected to isolation for a period not exceeding nine days from the time of arrival of the aircraft.

(c) A person coming from an area infected with yellow fever is not allowed to enter India, unless a period of nine days (six days incubation period *plus* three days when even in a symptom-free patient the virus may be present in the blood) has elapsed between the dates of his departure from that area and his arrival in India. If he arrives in India before the nine days have elapsed, he will be subjected for the balance of that period to isolation in a mosquito-proof ward to which he is conveyed in a mosquito-proof ambulance. Unrestricted admission to India from a yellow-fever-infected or a 'silent' area is however allowed to a person who is protected against the disease by a previous attack or by satisfactory inoculation. By satisfactory inoculation is meant that he must have been inoculated—

(i) not less than 14 days before his arrival in the yellow-fever-infected area, or in the alternative not less than 23 days before his arrival in India; and

(ii) not more than two years before his departure from the yellow-fever-infected area.

(d) Finally, aircraft are prohibited from entering India from the west except at Karachi where the organization for carrying out these measures exists.

The sanitary authorities in India have had a great fight with the international authorities to get these measures enforced in other countries, but they insisted on certain minimum requirements, which were eventually acceded to, and have been in operation for some years without much interference with international air traffic. These precautions do not provide an impassable barrier to the entrance of yellow fever, but they constitute a very effective one, and it is probably on them that India's immunity, up to the present, has depended.

It should perhaps be repeated that in no circumstances is one permitted to import yellow-fever virus into India, for any purpose whatsoever.

Aedes aegypti also transmits dengue, and the rapidity with which this infection spreads gives one some idea of how yellow fever would spread if it once gained a footing in India. Special measures are taken at aerodromes and in dock areas to control this species, as an extra precaution against yellow fever. In the event of an invasion by yellow fever, *aedes* control would have to be given priority over all other sanitary measures throughout the whole country.

Many people who are coming out to the East, including some coming to India, get inoculated in London before leaving, but wholesale inoculation has not been practised in India yet, though large stocks of vaccine are being held in readiness for an outbreak.

TREATMENT

There is at present no recognized specific for this disease, so that the treatment is essentially symptomatic. The extreme variability in the

severity of the disease accounts for the innumerable specifics that have gained local reputations.

The patient must be kept in a mosquito-proof room or under a net night and day during the first three days, and attendants must be inoculated. He should be confined to bed throughout the disease and for some days during convalescence. During the height of the fever the diet should be low and consist mainly of lime-whey, albumin water and barley water. Plenty of alkaline fluid should be given, sodium citrate or bicarbonate, by mouth, if possible, otherwise per rectum. Glucose should also be given liberally by mouth, and intravenously, a pint of 5 per cent solution together with five units of insulin.

The following prescription which is designed to reduce gastro-intestinal acidity is looked upon by some workers as a specific :—

R	Liquoris	hydrargyri	perchloridi	min. xii
	Sodii	bicarbonatis	gr. vi
	Aquam	ad	℥i

Take hourly.

Early purgation is recommended, $\frac{1}{4}$ grain doses of calomel half-hourly up to $1\frac{1}{2}$ grains, but later purgatives should be avoided.

Mouth hygiene is important to prevent stomatitis and parotitis; hydrogen peroxide is a useful mouth wash.

Other treatment is symptomatic :—

Vomiting.—Ten minims of adrenaline (1 in 1,000) by mouth, or $\frac{1}{4}$ grain of cocaine in an ounce of water.

Black vomit.—Liquor ferri perchloridi, ℥xv, to be repeated.

Hyperpyrexia.—This should be treated by hydrotherapy rather than antipyretic drugs.

Restlessness.—Phenobarbitone, gr. 1 to 3 by mouth or gr. 1 intramuscularly.

Anuria.—Dry cupping to loin, warm colon wash and warm citrate saline bladder wash, in addition to glucose and sodium bicarbonate intravenously.

Stimulants may be required in the later stages, especially during the 'period of calm' when collapse is not infrequent.

Convalescents should be treated cautiously, especially with reference to diet which should be increased very slowly; indiscretion may have serious consequences.

PROGNOSIS

The disease was at one time considered to be nearly 100 per cent fatal, but later it was realized that, in indigenous populations in particular, the infection often produced sub-clinical attacks, and that even Europeans in Africa suffer from mild attacks which may not be recognized. In most endemic areas, about 30 per cent of Europeans suffering from definite clinical attacks of yellow fever die; amongst others the death rate will vary considerably according to circumstances, but in semi-immune populations, it is undoubtedly sometimes a very mild disease, comparable to dengue both in its severity and in its clinical manifestations. In the recent epidemic in the Anglo-Egyptian Sudan, the mortality is reported to have been 10 per cent.

Finally, to emphasize the intensity of the disease and the inevitability of the issue when yellow fever takes its worst form, one cannot do better than re-quote Lins' perhaps rather too dramatic but very vivid description :

' . . . alkalis and acids, glucose and insulin, serum and blood of convalescent cases, transfusion of normal blood, anti-yellow-fever serum, specific vaccine therapy, bleeding, injections of iodine, of permanganate, of hyposulphite of sodium, of calcium, of chlorides, colloids, bismuth preparations, hæmostatics of

all kinds, and finally anti-tryptic serum in large doses, all were tried in vain against this terrible disease. Never did I observe beneficial effects from any one of these remedies; in not a single case did I have the satisfaction of believing that my treatment had improved the condition of this patient or that one, much less that it had been responsible for saving the life of this or that individual. The moribund whom I saw resuscitated were saved by a miracle and owe nothing to me; likewise, I owe nothing to the athletic young men I saw die, except the lingering remorse of having done nothing to save them . . . I tried innumerable times, but, accomplishing nothing, concluded at last that it was better to fold my arms rather than to contribute to the precipitation of the fatal outcome.'

REFERENCES

- FINLAY, C. (1881) *Ann. Acad. Ciencias*, **18**, 147.
 FINDLAY, G. M., and MACCALLUM, Vaccination contre la Fièvre Jaune au Moyen
 F. O. (1937). du Virus Pantrope Atténué Employé Seul.
Bull. Office Internat. Hyg. Pub., **29**, 1145.
 HINDLE, E. (1928) A Yellow Fever Vaccine. *Brit. Med. J.*, **i**, 976.
 KIRK, R., CAMPRELL, R. T., and Yellow Fever Infection as Observed in
 CHARLTON, R. (1941). Europeans in the Nuba Mountains, Anglo-
 Egyptian Sudan. *Ann. Trop. Med. and
 Parasit.*, **35**, 113.
 SAWYER, W. A., KITCHEN, S. F., and Vaccination of Humans against Yellow Fever
 LLOYD, W. (1931). with Immune Serum and Virus fixed for
 Mice. *Proc. Soc. Exper. Biol. and Med.*,
29, 62.
 THEILER, M. (1930) Studies on the Action of Yellow Fever Virus
 in Mice. *Ann. Trop. Med. and Parasit.*, **24**,
 249.

RIFT VALLEY FEVER

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Definition.—Rift valley fever is an epizootic hepatitis with a limited geographical distribution; in certain circumstances, it is transmitted to man in whom it causes a mild febrile disease.

Discussion.—The importance of this disease lies on the fact that it may be mistaken for mild yellow fever, because of its African distribution and because of the hepatitis. It is an example of a mild hepatitis caused by a specific filtrable virus, of which there are probably many other examples that have not yet achieved the distinction of a specific name.

Historical.—Though a very similar disease was encountered in this locality and described by Montgomery in 1913, the disease as it is now known was described by Daubney, Hudson and Garnham in 1931.

The epizootic was first recognized in 1912; the disease in man was common amongst the natives working with sheep and cattle, and it also occurred amongst the European veterinary personnel investigating the cause of the epizootic. The virus was brought to London where all the laboratory workers handling it developed the disease, and in New York a laboratory assistant is said to have died of the infection.

Epidemiology.—The disease is so far confined to the Rift valley in Kenya, and to those coming in contact with the infected cattle or sheep, or with the virus in the laboratory.

Ætiology.—The disease is caused by a filtrable virus, 23 to 35 $\mu\mu$ in size, which is found in the plasma and is attached to the red cells; it is present for six days after the onset of the attack, after which it is neutralized by antibodies that appear in the blood. The virus has an affinity for the nervous system. It does not appear in the urine.

It is transmitted through the mucous membranes or the scarified skin. Mosquitoes of the genus *Mansonia*, especially *Mansonia fuscopennata*, are suspected as carriers of the infection in nature.

Immunity.—There is immunity after an attack, which lasts for some years, certainly six, but is probably not permanent. In animals it lasts only about six months.

Pathology.—The morbid anatomy has been studied in animals. The most characteristic feature is a focal necrosis in the liver, at first discrete but eventually coalescing. There is a hyaline degeneration of the cytoplasm of the liver cells, and oxychromatic degeneration of the nuclei.

Blood picture.—There is a leucocytosis during the first 24 hours of the attack, and this is followed by a leucopenia with a relative increase in lymphocytes.

Symptomatology.—The incubation period is from four to six days; the onset is sudden, with rigors (often), malaise, nausea, headache and photophobia, backache, and a feeling of fullness in the liver region. The face is flushed, the tongue furred, and there is constipation. The temperature rises to 102°F. or higher, and falls rather suddenly about the fourth day, with profuse sweating. The disease runs a benign course, the mortality being almost nil, but there is marked weakness and a tendency to sweating during convalescence.

Diagnosis.—A diagnosis can be made by inoculating the blood during the first few days into mice, 0.1 c.cm. being given intraperitoneally; the mouse will develop an encephalitis in 48 to 72 hours. As many other viruses kill mice, the identity of this infection must be ascertained by including a control experiment in which the patient's blood is mixed with convalescent serum before injecting it into a mouse; the control mouse will not die if the virus is that of Rift valley fever.

A retrospective diagnosis can be made by the mouse-protection test (cf. YELLOW FEVER), or by a complement-deviation test, which remains positive for at least six months.

The disease has to be differentiated from influenza, dengue, sand-fly fever, other forms of hepatitis, and mild yellow fever.

Prevention.—A vaccine made from a fixed neurotropic virus has been used with success in prophylaxis in sheep.

Treatment.—No specific treatment for the condition has yet been discovered. The symptomatic treatment consists in giving glucose freely by mouth and intravenously. Convalescent serum is reputed to cut short an attack.

REFERENCES

- DAUBNEY, R., HUDSON, J. R., and Enzootic Hepatitis or Rift Valley Fever.
 GARNHAM, P. C. (1931). *J. Path. and Bact.*, **34**, 545.
 MONTGOMERY, R. E. (1913). .. *Ann. Rep. Vet. Dep., Kenya Colony*, 1912-13.
 Nairobi.

DENGUE SAND-FLY GROUP

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Introduction.—The two main clinical syndromes of this group are the mosquito-borne dengue, and the sand-fly-borne sand-fly fever. Both diseases are caused by filtrable viruses, are clinically characterized by short fever, a rash, severe pains in the joints and back, and headache, and are diseases of very low mortality. Megaw, who was one of the first workers to insist on the recognition of this group as a group—a procedure which provides, in the writer's opinion, a logical classification—tended to stress the similarities between the two and minimized the differences, and considered that there was some evidence for the identity, or at least the common origin, of these two viruses which, he suggested, might have acquired certain special characteristics by being transmitted by insects of different species.

Most workers, however, who have had experience of both diseases, recognize the clear differences in the syndromes, and consider the two as quite separate diseases, probably caused by two distinct viruses. Admittedly, it may be very difficult in any one particular case to be dogmatic and say this is definitely a case of sand-fly fever or of dengue, but, given half-a-dozen cases of each disease, it will usually be possible to say, quite definitely, which set is dengue and which sand-fly fever. Further, there is no evidence of the existence of any cross immunity.

Megaw postulates a third member of this group—dengue of unknown vector. Our knowledge of the short fevers of the tropics is certainly far from complete, and a possible example of another disease of this group is so-called Colorado tick fever, a dengue-like disease of virus origin which, mainly on epidemiological evidence, is thought to be transmitted by a tick

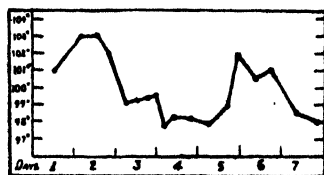


Figure 92: Temperature chart of Colorado tick fever (Topping *et al.*, 1940).

Dermacentor andersoni (Topping *et al.*, 1940). The dengue-like nature of this disease (*vide* figure 92) seems to be more certain than its suggested mode of transmission. We must realize that the future may add more members to this group, and it is more than justifiable to keep the classification an open one, but the inclusion at the present date of this entity 'dengue of unknown vector' in our classification will serve no useful purpose, and might imply the recognition of a single specific clinical syndrome whose full ætiology was unknown.

DENGUE

Definition.—Dengue is a short febrile disease of about 7 days' duration, characterized by severe pains all over the body, rashes, and a terminal rise of temperature. It occurs endemically and epidemically in the coastal areas of many tropical and sub-tropical countries. It is caused by a filtrable virus, and is transmitted from man to man by *stegomyia* (aedes) mosquitoes.

Historical.—Dengue has been recognized in various countries as a distinct disease for many years; an epidemic was reported in Cairo in 1779, but the disease was first described by Rush of Philadelphia, as 'break-bone fever', in 1780. Many epidemic outbreaks were reported during the next century, and the name 'dengue' was applied to it. The word is of Spanish origin, from *denguero*, an affected or dandified person, indicating the characteristic stiff or unnatural gait of the sufferer.

In 1903, Graham transmitted the disease by the agency of mosquitoes, which he described as *culex*. In 1907, Ashburn and Craig transmitted dengue in blood that had been passed through a filter. They experimented with *culex*, and claimed one transmission by this means. In 1916, Cleland, Bradley and McDonald conveyed the disease by aedes mosquitoes. A few years later, Siler, Hall and Hitchens (1924) in Manila confirmed these observations and demonstrated the whole transmission cycle (*vide infra*).

EPIDEMIOLOGY

Geographical distribution.—It has a wide, tropical and sub-tropical distribution in the four major continents, and it occurs in Queensland in Australia. In America, except for a few isolated epidemics, *e.g.* the Philadelphia epidemic, its zone of activity extends from Charleston in South Carolina to Sao Paulo in Argentina.

Its incidence is conditioned by the distribution of *aëdes*, and it is therefore confined mainly to coastal areas.

Epidemic features.—It is a disease of towns rather than country areas. It does not occur at an altitude of more than 6,000 feet and it is confined to the plains in the sub-tropical regions. In the tropics, it is endemic but subject to cyclical and seasonal exacerbations; in the sub-tropical and temperate zones it is usually epidemic (*e.g.* the epidemics in Dallas in 1897 and in Athens in 1927 when at least half the inhabitants suffered and the public services were temporarily dislocated).

Seasonal incidence.—In the sub-tropics, it is a late summer and autumn disease. In the tropics, it is variable, and again dependent on *aëdes* activity; in many places, it is perennial, but it tends to show a monsoon rise, and in Calcutta the highest incidence is in August and September.

Age, sex, and race.—All ages and both sexes are susceptible, but the disease is less prominent in children. All races are equally susceptible, but the local inhabitants nearly always enjoy some if not complete immunity through previous infection; it is always the visitors who are attacked. Every year we have half a dozen or more cases amongst our post-graduate students, and the patients are always the visitors to Bengal, though such students represent only a small percentage of the class.



Figure 93 : Seasonal curves of *aëdes* and dengue in Calcutta.

ÆTIOLOGY

The virus.—This is filtrable; it will pass through L_3 and L_5 Chamberland filter candles. It circulates in the blood for the first three days of the disease, after which it is neutralized by antibodies.

Transmission.—It is transmitted by *Aedes ægypti* (previously known as *Stegomyia fasciata*) which becomes infectious after biting a patient within the first three days of the fever; the virus undergoes development in the mosquito, which is capable of transmitting after the 8th day and remains infectious for the rest of its life. *Aedes* alone transmits, not *Culex*. In the Philippines *Aedes albopictus* is the transmitter.

Immunity.—An attack causes a certain amount of immunity, but not complete immunity. The first attack is usually a bad one; the second is a mild one; and the subsequent ones are usually abortive, amounting to little more than a feeling of malaise for 24 hours or less, and possibly being unnoticed. Recent work shows that there is no cross immunity with sand-fly fever or yellow fever.

PATHOLOGY

Dengue is not a fatal disease, so that little is known about the morbid anatomy.

The blood picture has certain characteristic features; there is marked leucopenia, which is a granulopenia. The Arneth count shows a marked

shift to the left. There may be a distinct leucocytosis following the attack, with the Arneth count still maintaining its leftward shift.

There is nothing characteristic in the urine; it is highly coloured and there is usually a trace of albumin.

SYMPTOMATOLOGY

The incubation period is usually 4 to 7 days. In extreme cases it may be from 2 to 15 days.

The onset is sudden, the temperature rising rapidly to 103°F. Although the temperature is very high, there is seldom a typical rigor. There is severe headache and pains in the eyeballs with marked photophobia, pain in the back, in the bones, and all over the body, causing the patient to assume a characteristic stiff gait when walking, and to toss from side to side in his bed. The tongue is furred and red at the tip. The face is flushed and the eyes are suffused. There is very often general glandular enlargement.

Other symptoms include constipation, or a 'critical' diarrhoea accompanying the second rise of temperature.

The fever varies considerably from case to case and from epidemic to epidemic, but there is a tendency for one type to predominate in each epidemic or seasonal exacerbation. The seven days' temperature is the classical form. The temperature remains high for two or three days, coming down slowly to about 99°, and then rises suddenly on the 6th or 7th day, and drops to normal again.

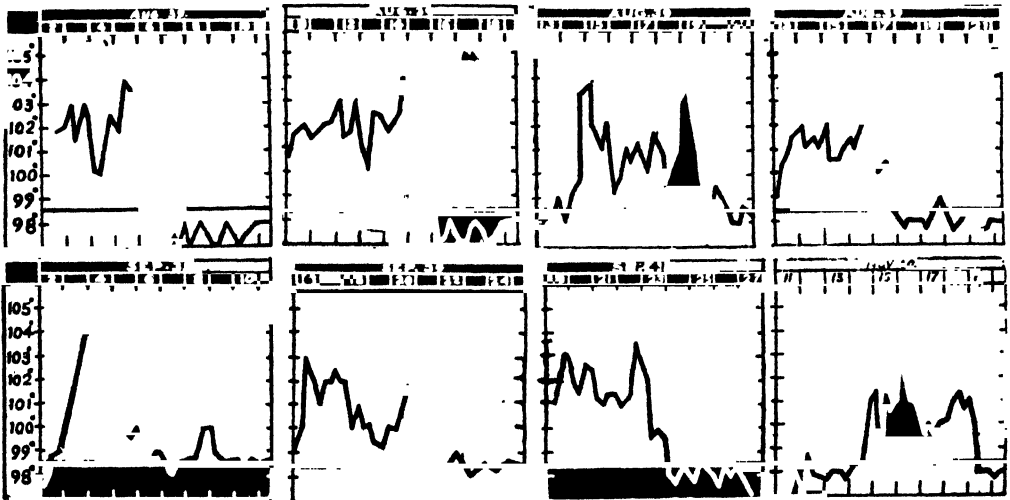


Figure 94 : Showing temperature charts of six consecutive cases of dengue, and two additional charts, the last being a hospital infection.

In the **continued type**, the fever maintains a high remittent character for the full seven days, and then drops suddenly. Sometimes there is quite a definite fall, with a few days of normal temperature before the final rise—the **two-phase type** of temperature chart.

In milder epidemics, there is only a single rise of temperature, a sharp rise for two days which then fades away. In this one-phase or **abortive type**, the second rise of temperature may be so slight that it is not noticed, or it may not occur at all.

In exceptional cases, the second rise is higher than the first one; there is a three-phase temperature; or there is a late relapse about the 15th day.

The pulse is usually rapid during the first few days of fever, but it may fall before the temperature falls, and after the attack it is often very low indeed, down to 40 per minute.

Rashes.—There are two distinct rashes; the primary rash which occurs at the onset is a transitory erythematous rash on the neck, face, shoulders and chest; and the secondary rash which appears about the fifth day or even after the fall of temperature on the 7th or 8th day. The latter is a macular or scarlatiniform rash, usually commencing on the hands and wrists or legs and extending to the chest, not usually to the face, but otherwise all over the body. It may be very irritating and in severe cases there is later marked desquamation.

Complications and sequelæ.—There are not usually any complications. The following are occasionally encountered: hyperpyrexia, hæmorrhages, diarrhœa, orchitis, and albuminuria. The sequelæ are not unimportant, though they are not common. They include acute depression amounting to definite melancholia, multiple joint pains, pain in one or two joints which may be very troublesome and last for two or three months or even longer, and a tendency to faint.

Variations in the symptomatology.—The different temperature charts that are encountered are discussed above; other symptoms, especially the rashes, show the same characteristic tendency to vary from epidemic to epidemic. That is to say, there are epidemics when rashes will appear only in 10 per cent of the cases, and others where they occur in 95 per cent; in some epidemics, pains are the most prominent symptom, whereas in others, they are only of secondary importance; and in some epidemics that troublesome sequel, arthralgia, is the rule whereas in others it never occurs.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis must be made on the clinical evidence and by a process of exclusion; there are no positive laboratory tests. The short fevers that have to be excluded include: sand-fly fever (*vide infra*); malaria—definite rigor, periodicity, and the finding of parasites; influenza—catarrhal symptoms and absence of rash; measles—catarrhal symptoms and Koplik's spots; scarlet fever—not common in tropics, sore throat; relapsing fever—absence of rash and finding of the parasites; and Japanese 7-day fever (leptospirosis). The more serious conditions include: yellow fever—usually of greater intensity with much albuminuria and jaundice; Weil's disease; small-pox; and typhus.

The severe pains might simulate rheumatic fever, and the rash, which is sometimes very intense, secondary syphilis.

PREVENTION

The only practical measure of dengue prevention is the control of *Aedes*. *Aedes* have a very limited flight, so that the elimination of their breeding places does not present very great difficulties, if properly organized. Spray-killing of the adult mosquito should also be undertaken, in both day and night quarters. Other measures should include screening and/or the use of mosquito nets, and the application of repellent substances to the ankles, wrists and other exposed parts of the body (*vide supra*, pp. 119 and 305).

TREATMENT

There is no specific treatment.

A salicylate mixture should be prescribed, and a brisk purgative, for example, $\frac{1}{4}$ -grain doses of calomel every half hour up to six doses followed by salts in the morning. Aspirin may be given in addition for the pains, and bromides or phenobarbitone for the sleeplessness. For persisting joint pains, local analgesic ointments or liniments, such as oil of wintergreen, should be applied, and a mixture containing tincture of belladonna and tincture of colchicum given.

Prognosis.—This is always good. In extensive epidemics, the death rate has been placed at about 0.2 per cent, the deaths occurring amongst old and debilitated persons.

SAND-FLY FEVER

Definition.—Sand-fly or phlebotomus fever is a fever of short duration characterized by headache, pain in the eyeballs and all over the body, and often by great prostration. It is caused by a filtrable virus which is transmitted from man to man by sand-flies.

Historical.—It has been recognized for a long time, particularly in India. It was known as febricula, pyrexia of unknown origin (P.U.O.), climatic fever, and by various other names. Pym (1804) described it as a separate entity. In 1909, Doerr, Franz and Taussig showed that—(a) it was a blood infection and that the virus was present during the first day only, (b) the virus was filtrable, and (c) *Phlebotomus papatasi* was the transmitter. In 1908, Birt showed that sand-flies cannot transmit for 7 days after the infecting bite. Shortt and others (1934) have shown that blood is infective on the second day of the fever.

EPIDEMIOLOGY

It has a wide geographical distribution in tropical and sub-tropical regions, but mainly in the latter; it occurs in the Mediterranean littoral including north Africa, Egypt and Palestine, in Syria, Iraq, Iran, north-west India, and central and south America.

It does not usually occur above 4,000 feet, and never above 7,000 feet.

It usually occurs in late summer and autumn (*vide* figure 95), but the incidence curve will vary in different localities. The sand-fly season in north-west India starts in April or May and lasts until October.

ÆTIOLOGY

The virus.—The virus is filtrable and passes through L_8 and L_5 Chamberland filters. It circulates in the blood one day before and during the first two days of the attack.

Monkeys can be infected.

Transmission.—It is transmitted by *Phlebotomus papatasi*, the golden-coloured sand-fly. The virus undergoes a stage of development in the sand-fly, during which it is not transmissible. Transmission will occur on the seventh day after the infecting feed, and the sand-fly remains infectious for the rest of its life. The virus is said to be transmitted to the next generation; possibly the larvæ become infected by feeding on the bodies of dead adults.

Immunity.—It is generally considered that immunity is complete, but in some places second attacks have been reported, even in the same season. There is no cross immunity with dengue or yellow fever.

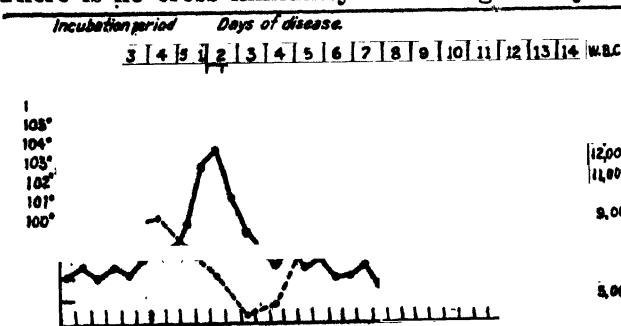


Figure 96 : Temperature chart with leucocyte count records in sand-fly fever (Whittingham, 1938).

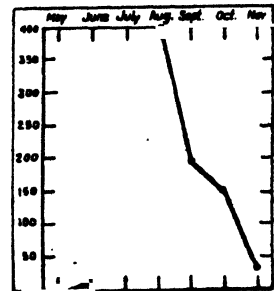


Figure 95 : Seasonal distribution of sand-fly fever in Palestine (Walker and Dods, 1941).

Pathology.—Sand-fly fever is not a fatal disease so that the morbid anatomy has not been studied. The blood picture shows a leucopenia followed by a sharp leucocytosis a day or two after the temperature falls (*vide* figure 96). The urine shows the usual febrile characteristics.

SYMPTOMATOLOGY

The incubation period is from 4 to 10 days, usually about 6 days. The onset occurs with a rigor. The average duration of the fever is 3 to 4 days, but it may be longer. A secondary rise is comparatively rare. The pulse is strikingly slow, often from the second day of the fever.

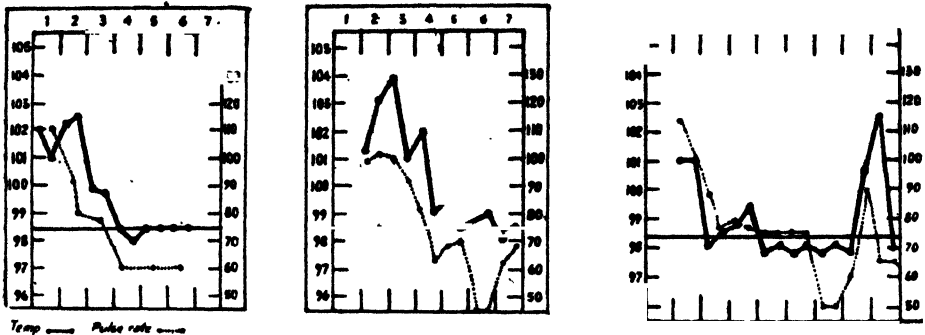


Figure 97: Three sand-fly fever temperature charts; the first two are typical; and the last is unusual and shows a terminal rise suggestive of dengue (Walker and Dods, *loc. cit.*).

There is a general puffiness, and uniform flushing of the face; the conjunctivæ are congested; there is restlessness, insomnia, and general prostration. The tongue is furred and there are often vesicles, unaccompanied by any inflammatory reaction of the mucous membranes, on the palate, but the fauces are congested. There are pains all over the body, very much the same as in dengue, but headache, photophobia, and tenderness and pain on movement of the eyeballs are probably relatively more intense. There is, in some epidemics, a sensation of an intense band-like restriction round the liver region, which suggests hepatitis, or severe hepatic congestion.

A rash is exceptional.

There may be general hyperæsthesia of the skin of the face, head and trunk, and absence of the biceps and supinator reflexes.

Papilloedema has recently been reported as constantly present in this disease in a severe epidemic in British soldiers (Shee, 1942).

Complications.—There are not very many complications, but a condition suggesting benign lymphocytic meningitis has been reported.

Diagnosis and differential diagnosis.—This is clinical and by a process of exclusion. The disease has to be distinguished mainly from malaria, dengue, and influenza; the complete absence of catarrhal symptoms helps in the last named. The author has seen a case diagnosed as small-pox, the

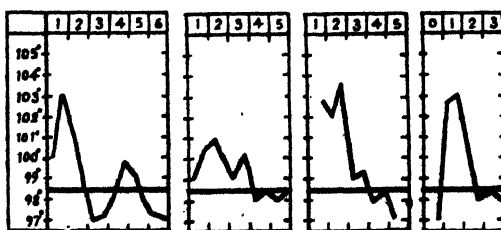


Figure 98: Sand-fly fever temperature charts from Peshawar (Anderson, 1941).

sand-fly bites on the forehead and wrists providing the characteristic shotty feeling.

The muscular pains and more especially the band-like pain around the lower part of the thoracic cage suggest Bornholm's disease. Sand-fly fever can be distinguished from benign lymphocytic meningitis, which it may simulate, by the low lymphocyte count in the cerebrospinal fluid in the former.

PREVENTION

Preventive measures are all aimed at the sand-fly. They can be summarized as follows :—

(a) The avoidance of localities that are heavily infested with sand-flies or from the nature of the terrain likely to be so infested at the favourable season.

(b) The elimination or treatment of their breeding places.

(c) The elimination or treatment of the resting places of the adult fly.

(d) Personal preventive measures against the bites of sand-flies.

(a) Much can be done by the proper choice of a camping ground especially by the avoidance of a 'cool' river bank; moving a bed or tent even a hundred yards may make all the difference. Top floors are preferable to ground floors, and open airy rooms to shut-in ones.

(b) The sand-fly requires, for its breeding place, darkness and protection from air currents, a comparatively even 'effective' temperature, moisture which also helps to maintain this temperature, and food in the form of some decaying animal or vegetable matter.

It has a very limited flight, so that it is only necessary to control the breeding places for a small area around the house or camp; a provisional figure of 120 yards is usually accepted for this. They breed in heaps of brick rubble, in old and dilapidated buildings, in the banks of rivers, streams, or ditches, in the internal or external cracks in any form of building, in disused fireplaces and chimneys, and even in the cracks in the dried earth.

Inhabited buildings should therefore be kept in repair and all cracks filled up before the sand-fly season. Where this is not possible for any reason, they can be treated with a mixture consisting of 10 per cent of naphthalene dissolved in kerosene—four pounds of naphthalene balls added to a 4-gallon drum of kerosene and allowed to dissolve for three days.

(c) Resting places for the adult flies should be reduced to a minimum by removal of curtains, pictures, superfluous furniture, and collections of clothes, and the elimination of all dark corners. Rooms should be fumigated or sprayed with any suitable anti-malarial fumigant or spray (see p. 8.) in the evening and closed for half to one hour after the fumigation. Unused fireplaces should have paper burnt in them nightly. Closed drains and culverts should be fumigated periodically with sulphur.

(d) Personal protection will include the use of nets of sufficiently fine mesh to keep out sand-flies—for this purpose the nets must be 45/46 mesh (see p. 119), or electric fans where these are available, the wearing of suitable protective clothing in the evenings, protection of the ankles by means of mosquito boots, and the application of repellent creams to the ankles and exposed parts of the body (see pp. 118 and 119).

Treatment.—This is mainly symptomatic. Aspirin, phenacetin and caffeine, or phenobarbitone in more severe cases, should be given for the pains and headaches. Dover's powder is useful, and Manson-Bahr considers that opium is a specific, recommending doses of 30 minims of the tincture.

Prognosis is uniformly good.

COMPARABLE FEATURES OF DENGUE AND SAND-FLY FEVER

Common.—They are short fevers with many common clinical features, are caused by filtrable viruses, and are transmitted by insects. The virus is present in the patient's blood for 3 days and takes about a week to develop in the insect.

Distinguishing.—These can be best shown in the form of a tabular statement :—

Dengue	Sand-fly fever
1. Virus present for first 3 days of fever.	Virus present day before fever and for the first 2 days after onset.
2. Transmitted by <i>Aedes aegypti</i> .	Transmitted by <i>Phlebotomus papatasi</i> .
3. Eight days' development in mosquito.	Seven days' development in sand-fly.
4. Mainly tropical.	Mainly sub-tropical.
5. Fever lasts 5 to 7 days usually, sometimes less. Secondary rise of temperature occurs in 25 to 80 per cent of cases in different epidemics.	Fever lasts 3 to 4 days usually, sometimes longer. Rare.
6. Primary rash occasionally; secondary rash all over the body, in most epidemics.	Rare.
7. Immunity is variable and tends to be short.	Immunity is usually complete.

REFERENCES

- ANDERSON, W. M. E. (1941) .. Clinical Observations on Sandfly Fever in the Peshawar District. *J. Roy. Army Med. Corps*, **77**, 225.
- ASHBURN, P. M., and CRAIG, C. F. (1907). Experimental Investigations regarding the Aetiology of Dengue Fever, with a General Consideration of the Disease. *Philippine J. Sci.*, **2**, 93.
- BIRT, C. (1908) .. Experimental Investigation of 'Simple Continued Fever'. *J. Roy. Army Med. Corps*, **11**, 566.
- CLELAND, J. B., BRADLEY, B., and McDONALD, W. (1916). On the Transmission of Australian Dengue by the Mosquito *Stegomyia fasciata*. *Med. J. Australia*, **ii**, 179 and 200.
- DOERR, R., FRANZ, K., and TAUSSIG, S. (1909). *Das Pappataci-fieber*. Franz Deuticke, Leipzig.
- GRAHAM, H. (1903) .. The Dengue, A Study of Its Pathology and Mode of Propagation. *J. Trop. Med. and Hyg.*, **6**, 209.
- SHEE, J. C. (1942) .. A Clinical Sign in Sandfly Fever. *Indian Med. Gaz.*, **77**, 732.
- SHORTT, H. E., POOLE, L. T., and STEPHENS, E. D. (1934). Sandfly Fever on the Indian Frontier. *Indian J. Med. Res.*, **21**, 775.
- SILER, J. F., HALL, M. W., and HITCHENS, A. P. (1925). Results obtained in the Transmission of Dengue Fever. *J. Amer. Med. Assoc.*, **84**, 1163.
- TOPPING, N. H., COLLYFORD, J. S., and DAVIS, G. E. (1940). Colorado Tick Fever. *Pub. Health Rep.*, **55**, 2224.
- WALKER, A. S., and DODS, L. (1941). Clinical Impressions of an Epidemic of Sandfly Fever in Palestine during 1940. *Med. J. Australia*, **i**, 345.
- WHITTINGHAM, H. E. (1938) .. *Phlebotomus* Fever. *British Encyclopædia of Medical Practice*, **9**, 583. Butterworth and Co., Ltd., London.

PLAGUE

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Definition.—Plague is an endemic disease that frequently develops epidemic proportions and spreads widely; the causal organism is the plague bacillus, *Pasteurella pestis*, an organism that produces a severe epizootic amongst certain rodents from which the infection is transmitted to man by the agency of fleas; the clinical picture is characterized by high fever, adenitis, a rapid course, and a high mortality, or the disease may take a pneumonic form with a cent-per-cent mortality.

Historical.—Plague is a disease of great antiquity. It has apparently been endemic for many centuries in certain areas of Asia. Kumaun and Garhwal in India; the Yunan province of South China, and the hills of South Arabia are considered endemic areas of very long standing.

Regarding the ancient history of plague in Asia, relatively little is known, but it is considered that ancient, as well as the more recent, pandemics arose in Asia. In Europe more is known of its history; Homer describes plague as occurring at the siege of Troy in the 12th century B.C. The cause was thought to be the wrath of Apollo at the untidiness of the camp, and, when Agamemnon ordered all the rubbish to be collected and thrown into the sea, Apollo's wrath was appeased and the disease disappeared.

Plague was described by various writers in the classical period as occurring in the countries around the eastern Mediterranean. The Justinian pandemic of 543 A.D. is said to have reached Europe from Egypt and spread throughout the Roman Empire along the lines of human communication. The greatest European epidemic, however, was the Black Death starting in 1346 A.D. It is reported to have reached Europe from the near east; it spread all over Europe and

adjacent countries, and killed, we are told, one-quarter of the population of the then-known world. References to this great outbreak occur in the histories of many countries. Another European epidemic occurred in the ten years following 1664, and in London about one-sixth of the population is said to have died in the first two years. These were only the great visitations of plague, and actually plague was never absent from Europe between the 14th century and the beginning of the 19th century; in the years between the great pestilences many minor outbreaks occurred.

The third great pandemic of the present millenium started in 1894 and is now apparently drawing to its close. It originated in Yunan province in China and rapidly spread to Hong-Kong, Japan and the Philippine Islands. In 1896 it appeared in Bombay which had been free from plague for nearly two hundred years, and thence it spread over most of India. From India it spread to Africa and to Australasia (1899), Hawaii, Central and South America (1899), to the United States (San Francisco, 1900), and to a limited extent to Europe. This pandemic involved almost the whole world; India, however, suffered most. In some of the early years of this century the deaths from plague in India numbered over a million, and in 1907 they reached a peak of nearly 1½ millions, since when they have steadily declined.

In the United States, on the other hand, from the time of the first introduction of the disease in 1900 to 1941, only 501 cases with 316 deaths have been reported. These cases have occurred in eight states; the first appearance of the disease was as follows:—California, 1900; Washington, 1907; Louisiana, 1914; Florida, 1920; Texas, 1920; Oregon, 1934; Utah, 1936; and Nevada, 1937. Up to January 1942, the last two human cases reported occurred in Siskiyou County, California, in June 1941.

EPIDEMIOLOGY

Geographical distribution.—Plague is now endemic in India, Burma, Ceylon, Java, China, and Madagascar, in South, Central, and East Africa including Uganda and Kenya, and in Senegal; sporadic in Iraq, Iran, Siam and French Indo-China. In South America, in Ecuador, Bolivia, Peru and Argentina, there are endemic foci. In California and certain other western states, epizootics are common but few human cases have occurred. In Europe, including Great Britain, local rat epizootics have occurred in ports from time to time during the last forty years, occasionally with a few secondary human cases.

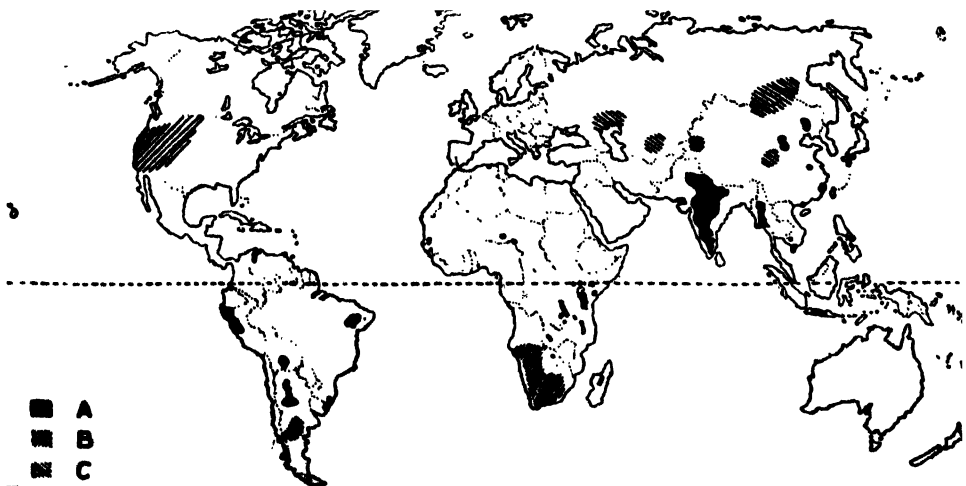


Figure 99 : World plague situation in 1937-38.

- A. Active foci of human plague.
 - B. Active foci of selvatic plague with occasional human cases.
 - C. Important foci of selvatic plague apparently quiescent at present.
- (Reproduced from League of Nations' *Epidemiological records*.)

In China, it is now mainly confined to western Shansi province where the Yellow River flows between this and Shensi province, in which some foci of infection are also present, to Fukien province where in the mountainous areas pneumonic plague also occurs, and to Manchuria. In the first two areas the rat is the main reservoir, whereas in Manchuria other rodents, the marmot or tarabagan, are responsible and the disease is more sporadic, but very liable to develop into a pneumonic epidemic.

In India, it is still endemic in the Bombay Presidency, in Hyderabad and Mysore States, in the Madras Presidency, in Bihar, the United Provinces and in a few other localities in central and northern India. In Bengal and Assam, no plague has occurred for many years, and in the eastern and southern parts of Madras it is comparatively rare.

Epidemic features.—Recent studies in plague have shown that there are two main epidemiological groups, (a) urban and domestic plague and (b) selvatic plague, and that in each of these epidemiological groups the disease may develop from the bubonic to the pneumonic form, when its epidemiology will undergo a corresponding change.

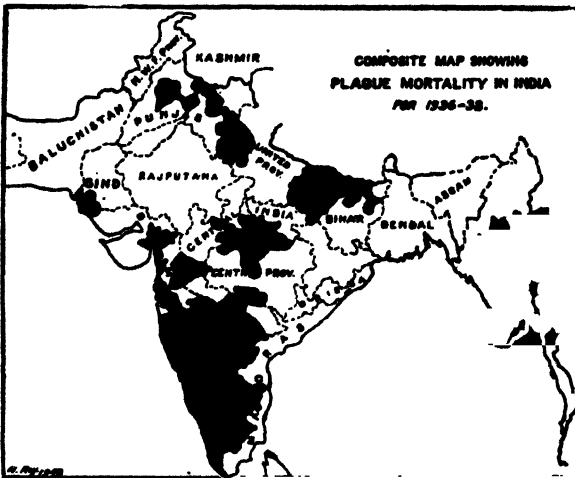


Figure 100 : In the black areas the annual plague mortality was over 0.1 per mille during at least one of these years.

The urban and domestic form (transmitted from rats) occurs in densely populated areas, and spreads along trade routes and overseas in ships. It is primarily bubonic and endemic, but bubonic plague may assume epidemic proportions and spread like an epidemic disease, though, as will be shown below, it is not a truly epidemic disease*.

In certain circumstances, probably connected mainly with the atmospheric temperature as it occurs most frequently in cold countries, pneumonic forms appear and the disease takes on a truly epidemic

form, being transmitted directly from man to man.

*The author is aware that here he is endowing the word *epidemic* with a special meaning that it does not always convey. The *Oxford Dictionary*, quoting from the *Sydenham Society Lexicon*, gives the meaning as 'Prevalent among a people or a community at a special time, and produced by some special causes not generally present in the affected locality'. This admittedly allows a wider meaning, but if one goes back a little further to its earliest use (according to the *Oxford Dictionary*) one finds a more restricted meaning. Bacon (1622): 'It was conceived not to be an epidemick disease, but to proceed from a malignity in the constitution of the air'.

Language is a living thing, and it must be continually growing and changing. Bacon's conception of an 'epidemick' disease as being possibly a divine punishment, a curse, or a spell, upon the people, entirely independent of environment, could not be upheld and the Sydenham Society gave the word a wider meaning. To-day our knowledge about epidemic disease is more precise, but the word *epidemic* has lost its precision; its meaning certainly goes far beyond that given to it by the Sydenham Society, for we have epidemics of malaria in countries where the disease has occurred continuously for a thousand years. We must therefore invent a new word or define and restrict the meaning of the old one.

Selvatic plague (transmitted from wild rodents) that occurs in rural areas and amongst workers in the woods and fields is primarily a sporadic, bubonic plague, but is even more apt to develop into the pneumonic form, when it may be the starting point of a serious pneumonic epidemic (*e.g.* the Manchurian epidemics of 1910-11 and 1920-21 in which there were about 50,000 and 10,000 deaths, respectively).

Seasonal and year to year incidence.—Temperature and humidity have a marked influence on the spread of plague. A moderate temperature, 60°F., and a moderately high relative humidity, indicated by a saturation deficiency of less than 10 millibars (= relative humidity of over 60 per cent at 70°F., over 71 per cent at 80°F., over 79 per cent at 90°F., and over 85 per cent at 100°F.), are the most favourable. Consequently, the disease will tend to occur in the summer months in cooler climates (all the classical plagues in England reached their peaks in August), in the spring months in hot dry climates in the sub-tropics (*see* Punjab seasonal curve), and in tropical countries in which the temperature is more constant throughout the year, the plague-incidence curve will follow the humidity curve (*see* Bombay seasonal curve : figure 101).

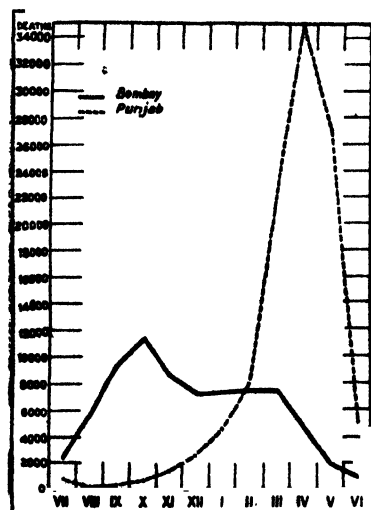


Figure 101: Monthly plague incidence, 1898-1931.

As well as the periodic epidemic-like waves of plague, in the production of which many factors are involved, there are in the endemic areas from year to year considerable variations in the incidence, which are associated with climatic variations, and Rogers (1933) has shown that, by studying the past meteorological data, it is possible to forecast whether it will be a good or bad plague year; long spells of abnormally hot and dry weather tend to reduce the incidence during the next plague season, and *vice versa*.

Age, sex, and race incidence.—In the urban and domestic bubonic form, persons of all ages and both sexes are equally susceptible, and there does not seem to be any racial immunity. In the pneumonic form, adults, both men and women, who attend the sick, and in the sporadic selvatic form, men, who are more likely to come in contact

with the sources of infection, are most frequently attacked.

The definition of an epidemic (*trans* : upon the people) that the writer has adopted for his own use is 'an outbreak of a disease that is transmitted from man to man, directly or indirectly, but in the transmission of which man forms an essential link'.

Application of this restriction on the meaning of the word *epidemic* does not entail interference with established nomenclature of disease, since diseases to which the word *epidemic* is regularly attached in a defining sense, *e.g.* epidemic typhus, are epidemic diseases in the restricted sense, and so-called 'epidemic dropsy' is a misnomer, already overdue for renaming, which is only awaiting a definite decision regarding its aetiology.

It would be rational to define *endemic* (*trans* : in or amongst the people) on the same lines, and to use the word *sporadic* when the disease did not comply with the restriction that 'man forms an essential link'. But the word *endemic* is already too deeply involved in disease nomenclature, *e.g.* 'endemic typhus' which is not an endemic, but essentially a sporadic, disease according to the suggested definition.

The writer has therefore not applied this restriction to the word *endemic*.

All these epidemiological observations are explainable on the grounds of the known ætiology of the disease which is discussed below.

ÆTIOLOGY

Historical.—The causal organism, *Pasteurella pestis*, was first isolated by Yersin who was working in Hong-Kong, in 1894.

The causal organism. Morphology and staining.—*Pasteurella pestis* is a small straight ovoid organism 0.7 by 1.5 μ , which shows a high degree of pleomorphism; it is non-motile, non-sporing, gram-negative, and shows bipolar staining.

Culture.—It is an aerobe and a facultative anaerobe. It grows easily on ordinary culture medium, producing very small round colourless transparent granular colonies in 24 hours at 37°C., increasing to large (4 mm.) raised opaque but translucent granular colonies in 5 days.

In broth it produces little or no turbidity in 24 hours, but later a flaky deposit; a delicate surface pedicle forms, and, if sterile oil is floated on the surface, 'stalactites' grow down from the under-surface of the oil globule.

There is no hæmolysis on blood agar.

Resistance.—These organisms are killed by drying at room temperature in a day or two, by heat at 55°C. in 5 minutes, and by 0.5 per cent phenol in 15 minutes. They survive in the cold almost indefinitely.

Distribution in the body and routes of escape.—Plague bacilli invade the skin, causing vesicular or pustular lesions, the local lymphatic system, causing buboes, and the blood stream, in this order; the infection does not however reach and persist in the blood in every case, but when it does the bacilli can naturally be found in every organ in the body. Under certain conditions, the lungs become the site of an intensive infection.

In the ordinary septicæmic infection the bacilli do not escape from the body in any of the normal secretions or excretions, but in the pneumonic form they escape in droplets during forced expiration.

Susceptible animals.—Man and both laboratory and wild rodents, and also monkeys are very susceptible; dogs, cats, cattle, sheep, goats and horses are difficult to infect; but most birds are immune.

Toxins.—No true exotoxin is formed, but bacillary filtrates cause severe toxic reactions and immune serum can be prepared by injecting animals (horses) with killed or living cultures.

Transmission

Historical.—In the historical records of plague epidemics in many countries, it was noted that rats began to die before human beings were affected, and the outbreaks in rats and in man were regarded as being intimately connected. The early investigators at the end of the last century failed to follow up this obvious lead and the first Indian Plague Commission (1901) went so far as to state categorically that there was no evidence that the disease was carried by infected rats in ships. In 1897, however, Ogata suggested tentatively that the flea might play a part in transmission, and in 1898 Simond working in Bombay enunciated the main facts about the transmission, epidemiology and control of plague which have remained practically unmodified, to the present day.

Lowe (1942) summarizes Simond's contribution to the transmission problem, as follows :—

'He stated that the introduction of plague-rats into a healthy area was generally followed by an epidemic of plague in man, but that introduction of an infected man into a healthy area was often not followed by an epidemic. He found that the epizootic preceded the epidemic, that it was usually localized in one area of a town to begin with, and that human plague later started in that particular area.

He noticed that in about 5 per cent of human cases a primary lesion in the form of a blister containing plague bacilli was seen, and recorded the site in the body of many of these blisters and found that they were most common on the

foot and leg. He considered that the blister was probably at the site of the bite of the transmitting insect. (This is the only observation for which he is usually given credit.)

He then went on to study the parasites of the rat. He found that a plague-rat free from parasites could not transmit the disease to healthy rats kept in the same cage but that a plague-rat infested with parasites could and usually did transmit the disease to healthy rats. He studied the parasites of the rat, the flea and the louse, and he found that these, particularly the flea, contained numerous ingested plague bacilli in their intestinal tracts. He crushed infected fleas and injected the material into rats and produced the disease. He therefore considered that the mode of transmission of plague was from rat to rat and rat to man by an infected parasite, most probably the flea. He found that infected fleas, while feeding, passed plague bacilli in their excreta and considered that the infection might be introduced at the time of the bite and into the site of the bite. [According to Nuttall (1899), one of his severest critics, he "does not directly claim that the fleas inoculate the bacilli by means of their proboscides, but he certainly implies it".] The only point he did not record was the phenomenon of the blockage of the proventricular valve with regurgitation of infected blood in attempts to feed, which was actually not recorded until sixteen years later by Bacot and Martin (1914).

He found that fleas remained infected for a considerable period and suggested that this fact might help to explain the carrying over of plague from one season to another. He found that, in cities where plague had been present, rats showed a relatively high degree of immunity to plague. He also suggested that variations in the rat population and in their susceptibility to plague played an important part in causing the periodicity of plague. He ascribed the decline and disappearance of the infection in an area to the death of a large part of the rat population, to migration of others, and to a high degree of immunity of the remaining rats, and thought that repopulation of the area by new strains of susceptible rats might cause recrudescence. He also believed that plague might continue to linger among rats in a benign form in the period following an epidemic and that sporadic cases in man might thus be explained.

He stated that the prophylaxis of the plague must be based on the destruction of rats and also of their parasites and on the prevention of the access of rats to human habitations by proper construction or reconstruction. He stated that the conveyance of plague from one country to another on ships could be prevented by the destruction of not merely the rats but of the rats' parasites in ships, and advocated the use of poison gas for this purpose.

Gauthier and Raybaud (1902) narrowed down the issue and transmitted plague from rat to rat by means of the bite of fleas.

Simond's work was confirmed by the Plague Investigation Commission (1904 to 1913); these workers amplified Simond's work, but added little of basic importance to it.

The *primary* transmission cycle of infection is rat-flea-rat. The flea becomes infected from the blood of an infected rat, and transmits the infection to another rat by its 'bite'. There are a number of other rodents that are capable of playing the part of the rat in the transmission cycle.

The infection of man is an off-shoot from this primary cycle, and normally, from the bacillus's point of view, man constitutes a *cul-de-sac*. Man is capable of constituting a link, but, as only very rarely are bacilli present in human blood in sufficiently large numbers to infect fleas that ingest his blood, and, as the fleas that normally infest man, *e.g.* *Pulex irritans*, are not good transmitters of plague bacilli, man constitutes a very weak link in the mammal-flea-mammal cycle of bubonic plague transmission. Bubonic plague is thus never truly epidemic though the disease may assume epidemic proportions (see footnote, pp. 324 and 325).

In certain circumstances, probably mainly associated with climatic conditions or other prevalent infections, plague bacilli become localized in the lungs and produce a pneumonia; when this has once occurred the *Pasteurella pestis* strain involved appears to acquire a pneumotropism, and subsequently droplet infection from man to man will take place and a true epidemic occurs. Primary pneumonic plague has in some localities been attributed to inhalation in dust of the faeces of infected fleas.

Infection may also take place *via* the alimentary tract, e.g. in Manchuria, infection has been caused by the eating of under-cooked infected marmots, and in South America in certain tribes it is the practice to kill fleas by biting them between the teeth, whilst other primitive people kill rodents by biting off their heads; in both these cases, infection may be acquired, but such exotic means never play any significant part in the epidemiology of the disease.

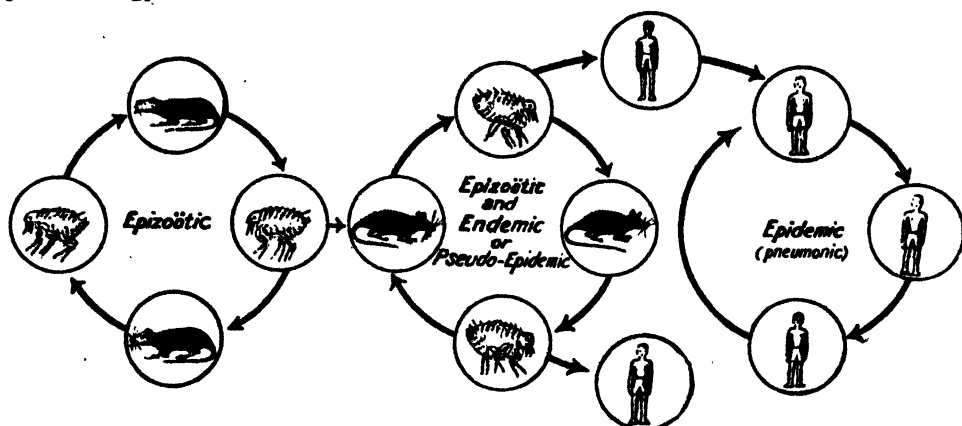


Figure 102: The transmission cycles in plague infection.

Left-hand cycle. Brown-rat—flea epizootic cycle.

Middle cycle. Black-rat—flea epizootic cycle, from which man is infected sporadically.

Right-hand cycle. Man to man epidemic cycle of pneumonic plague.

Infection has been acquired at a post-mortem examination and in the laboratory.

Finally, the bacillus has been injected with homicidal intent; such an instance occurred in Calcutta in 1933, when two accused, including one doctor, were convicted of murder.

Essentials for transmission of bubonic plague

The four essentials for the transmission of bubonic plague are thus :—

1. *The plague bacillus.*
2. *The rat or other rodent—the natural host and reservoir of infection.*
3. *The rat-flea or other flea vector.*
4. *Man, the alternative host, and his association with rats and fleas.*

Given plague infection (1), the incidence of the disease will depend on variations in the other three factors with regard to density of population (of 2 and 3), susceptibility (mainly of 2 and 3), and environment and habits (of 2, 3, and 4).

1. **Plague bacillus.**—*Pasteurella pestis*, as far as present-day knowledge goes, appears to be a comparatively homogeneous bacillus with regard to virulence, and the variations in the severity of epidemics can usually be attributed to other factors. It is however noticeable that in places where the disease is transmitted from rodents other than the rat, e.g. the marmot, it is often more severe and is more apt to develop into the pneumonic form, but in the determination of pneumotropism, the climatic factor cannot be excluded since these places are nearly always cold ones. An exception to this rule was the Los Angeles outbreak in 1924–25, when there were 33 pneumonic cases with 31 deaths; the reservoir was certainly the ground squirrel, but even here the epidemic occurred in mid-winter.

2. **The rodent.** *Species.*—There are two main groups of rodents involved in plague transmission, (i) rats which, in a general way, live in close association with man—though some species live in closer association than others—and are the rodents responsible for the epidemic-like

outbreaks, as well as being capable of maintaining endemicity, and (ii) wild rodents which are the reservoirs of infection in selvatic plague.

(i) The two species of rat most frequently involved in plague epizootics are the black domestic rat, *Rattus rattus*, and the large brown (grey) sewer rat, *Rattus norvegicus*. Rats of other genera, *Gunomys* and bandicoots, are also susceptible, but from their habits are a less important menace to man.

(ii) The tarabagan or marmot (*Arctomys bobac*) and several species *Citellus* (Susliks) in the Caucasus, Siberia and Manchuria, the jerboa in southern Russia, the gerbille and the multimammate mouse, *Mastomys coucha*, in Africa, and the ground squirrel (*Citellus beecheyi*) in California, are the most important reservoirs of selvatic plague.

The rat-factors determining incidence: these are—

(a) *Susceptibility and immunity*, natural and acquired; for the rodent to be an effective reservoir, the plague bacillus must be present in relatively large numbers in its blood. The degree of septicæmia will vary according to the susceptibility of the rat, which will depend on the species and past experience of the rat population.

(b) *Habits*; the reservoir of infection must come into close association with man, by natural inclination and/or by opportunity. This factor will depend on the species again, and on the environment.

(c) *Density of the rat population*; the disease will not assume epidemic proportions unless there is a sufficient number of susceptible rats living in close contact with man. The rat index, calculated from the number of rats caught in a given time in one hundred standard traps, must be at least 50. The rat index will depend on environment and food supply.

The development of conditions for an outbreak of plague in man.—

The usual sequence of events is as follows:—The grey rat, which travels in ships and generally from his habits makes more contacts with the outside world, is the first to become infected; one such rat acquires plague and dies; its fleas leave the dead body and parasitize other rats to whom they transmit the infection; and so a *grey-rat epizootic* develops. In time, a certain number of fleas from the plague-infected grey rats infest the more venturesome amongst the black rats and the *epizootic spreads to the domestic-rat population*. Infected fleas are thus brought into man's habitations, and, when the rat population becomes reduced, the fleas from a dead rat, failing to find another rat, begin to infest man, and when this incident is repeated many times, an outbreak, which assumes *epidemic proportions*, occurs amongst the human population (see figure 103).

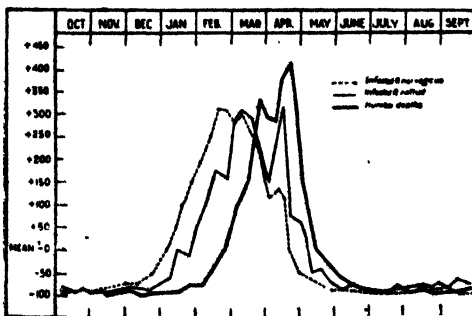


Figure 103: The development of a plague outbreak in man.

In course of time a point arrives when the whole rat population has been infected, a large number have died and the rest have recovered and are immune, so that the epizootic and the human outbreak come to an end. Epizootic conditions cannot arise again until a new generation of non-immune rats grows up. However, over a period of years, the rat population acquires a considerable degree of immunity; at one time it was suggested that this was achieved by passing the immunity on to the

next generation, but this is not usually accepted as possible, and it is thought

to be by a process of elimination of the more susceptible members of the community. In these circumstances the disease usually remains *endemic*.

Unless there is a considerable population of *R. rattus*, plague is never transmitted to man to any serious extent, and it is suggested that the replacement of the *R. rattus* population by *R. norvegicus* in many European countries, which started in the 17th century, accounts for the failure of plague to establish itself in these countries during the last two centuries, though it has been widespread in other countries where *R. rattus* still abounds. Again, in Bengal the predominant rat is not *R. rattus* (13 per cent), but *Gunomys varius* (28 per cent) and the bandicoot that are not so susceptible to plague, nor do they live inside houses; consequently plague is rare.

Another theory regarding the relative immunity of the Bengal rats to plague infection is that they have in the recent past suffered another pasteurella epizootic which was less fatal than *Past. pestis*, and that this pasteurella has in its antigenic structure some elements common with *Past. pestis*.

The most effective method of control of plague is by reducing the rat population, but this presents considerable difficulties as it has been reported that a single pair of rats can produce 858 progeny in 16 months.

The important factors here are harbourage and food supply; where houses are built so as to exclude rats, and all sources of food supply are kept out of their reach, the domestic-rat population will be low, and, conversely, where houses are mainly constructed of wood or some other soft material and where domestic garbage is thrown out without regard to sanitary and domestic tidiness, as in many Indian towns and villages, conditions are ideal for rat multiplication and the stage is set for the type of explosive outbreak that occurred in the early years of the present century (*cf.* the history of plague in India and the United States, p. 323).

Bengal owes her relative immunity from rat infestation, not to sanitary tidiness (far from it), but to the periodic flooding of large tracts of country and to the high sub-soil water level which prevents rats burrowing deeply into the ground, as well as to the innumerable competitors for garbage, some of which are the rat's natural enemies, *e.g.* crows, cats, jackals, and pariah dogs, which abound in all towns in Bengal.

In Manchuria, where the marmot is the wild rodent concerned, this rodent is not killed by plague infection, and, though it may infect a large number of fleas, it does not die, and the fleas do not leave it, so that by this means the infection does not spread rapidly and acquire epidemic proportions, but remains endemic. Further, this rodent does not normally come into close association with man. However, sporadic infections thus acquired are apt to be grave ones and frequently develop into pneumonic plague, and as such may be passed rapidly from man to man and constitute an epidemic.

A third set of conditions exists in California where the ground squirrel suffers epizootic visitations of plague, yet little human plague has occurred; there have only been 8 cases in the last 10 years*. The danger here is

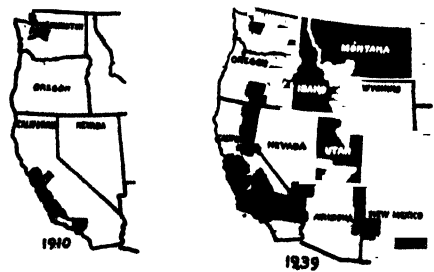


Figure 104: Showing extension of known areas of plague infection in the western states of the U. S. A.

* Later, in 1941, two human cases of plague were reported from Siskiyou County, California, whereas 44 instances of plague-infected rodents from California, and 13 from 7 other States in the U.S.A. were reported during the year. (*Pub. Health Rep.*, 1942, 57, 903.)

that fleas from these squirrels should be taken into the houses by other rodents, which are themselves perhaps not susceptible, or by domestic animals, or that an epizootic should arise amongst rodents that do frequent human inhabitations. For these reasons large sums of money have been spent on rodent destruction in that country.

3. *The flea. The mechanism of transmission.*—The flea ingests the blood of an infected rat (its capacity is about 0.5 c.mm. and this amount of blood may contain thousands of *Past. pestis*), and the plague bacilli multiply in its mid-gut; bacilli are passed in the faeces of the flea, and these may get scratched into the wound, but, as the bacilli are susceptible to drying, it is improbable that dried faeces disseminate the infection in dust. The infection in the flea's gut also passes forwards and eventually a massive infection may block the pharynx of the flea. When the flea attempts to take another blood meal, the blood will not pass this plug of bacilli, which have to be ejected by a regurgitatory effort; and the bacilli are thus injected *via* the flea's proboscis into the new host. A third method by which the flea transmits the infection is by contamination of its mandibles whilst feeding on an infected host, and direct transference of the *materies morbi* to another host. Of these three methods, the second is almost certainly the most important.

Only a comparatively small percentage of fleas feeding on an infected rat will become infected, and of those that become infected only a small percentage will transmit the infection; the percentages vary according to circumstances.

The flea-factors determining incidence : these are—

(a) *Efficiency of the flea as a transmitter*; which will vary according to (i) species and (ii) environmental (climatic) conditions under which it lives.

(b) *Longevity of the flea and maintenance of infection*, which is again a matter of climate and environment; in certain circumstances, the flea will live at least 45 days and will maintain plague infection for this period.

(c) *Feeding habits of the flea, zoöphilic or anthropophilic*, to which theoretically important factor not much significance seems to have been attached, probably because little difference in the various species has been demonstrated, most fleas being zoöphilic but prepared to feed on man in the absence of a better source of food.

(d) *Density of flea population*, which will depend on the climate and the rat population, varying directly with the latter; this is measured by a **flea index**, which gives the average number of fleas on each trapped rat; a **cheopis index** of at least 3 appears to be necessary for epizootic conditions.

(i) **Species.**—The most important transmitter of rat-borne plague in the tropics is *Xenopsylla cheopis*: Another rat flea, *Xenopsylla astia*, also common in the tropics, is capable of transmitting plague but is a relatively poor transmitter, and when this flea predominates plague seldom reaches epidemic proportions. Further, it does not sustain the infection for long, so that in endemic areas the disease is not carried over to the next season. Another relatively poor transmitter is *Xenopsylla braziliensis*. (The low incidence of plague in Madras is attributed to the low *cheopis* index, *X. astia* being the common flea.)

In temperate countries, *Ceratophyllus fasciatus* and *Leptopsylla segnes* are the important transmitters.

Pulex irritans, the flea that commonly infests man, is capable of transmitting the infection (*vide supra*), as are many other fleas such as the dog and the cat fleas, *Ctenocephalus canis* and *Ctenocephalus felis*.

The other rodent carriers have their various fleas, most of which will in special circumstances bite man and are capable of transmitting plague.

For example, *Ceratophyllus tesquorum* of the marmot will show the 'blocking' phenomenon, if fed on an infected animal; *Dinopsyllus typhus* and *Xenopsylla eridos* of the gerbille and other small African rodents, and *Ceratophyllus acutus* of the Californian ground squirrel are potential transmitters.

(ii) **Environmental (climatic) conditions.**—These have a marked effect on the flea. *X. cheopis* breeds best at a temperature between 68°F. and 77°F., and in the presence of a high degree of humidity. Above 85°F., not only does breeding slow down, but this high temperature adversely affects plague-infected fleas, so that, as the temperature rises, transmission decreases and eventually ceases. Humidity is also an important factor, and in the tropics a saturation deficiency of less than 10 millibars is necessary for effective transmission; under dry conditions 'blocked' fleas rapidly die. Thus, high temperatures and humidities, through their effect on the flea, are inimical to plague, a fact that influences its distribution and seasonal incidence. However, the surface atmospheric temperature is not always the important one, and it has been shown that, in deep rat burrows, temperature and humidity may remain suitable for flea survival and transmission of infection long after the surface atmosphere has become quite inimical to both. It is believed that it is by this means that infection survives the hot dry season in some places (George and Webster, 1934). Conversely, in cold countries, fleas may find micro-climates, e.g. in houses and in ships, which are warm enough for them.

Where other fleas are the transmitters, the ranges of temperature and humidity ideal for propagation and to some extent for transmission may be different, but the same general principles will apply.

4. **Man and his environment.**—There is little evidence of any differences in the susceptibility of different populations.

The density of the human population will of course influence the actual number of cases in a particular area, but overcrowding will only lead to an arithmetical, and not a geometrical, increase, as would be the case in a truly epidemic disease (see footnote, p. 324). As, however, overcrowding is usually associated with insanitary conditions in which rats are likely to flourish, it may indirectly assist transmission. If man's environment is such as to provide harbourage and food for rats, and to encourage a close association between rats and man, the conditions will be favourable for a plague outbreak should the infection be introduced.

To summarize.—Plague will be maximal when the infection is introduced into a locality where conditions are most favourable, that is, where *R. rattus* is the predominant rat and is abundant, where *X. cheopis* is the predominant flea and climate conditions favour its rapid propagation and longevity, and where the human population lives crowded together in towns under very insanitary conditions; it will be sub-maximal when any of these sets of conditions is unfavourable; and it will probably be absent when any one of them is very unfavourable, and will certainly be absent if all of them are unfavourable.

Spread of infection outside endemic areas

This is effected by either rat or flea migration; human migration *per se* plays no part in the spread of infection.

R. rattus seldom migrates any distance voluntarily, but may be carried by sea, rail, river, or road transport in merchandise. *R. norvegicus* is a more ready traveller. Wild rodents are believed to migrate long distances.

The ability of the flea to survive in grain bags, gunnies, etc., for long periods, even under unfavourable external atmospheric conditions, has only recently been fully appreciated, and it is believed that this mode of

transfer of infected fleas plays an important part in carrying infection from place to place.

PATHOLOGY

General reaction to infection.—There are three lines of defence against the invading bacillus : (a) the skin, (b) the lymphatic glands, and (c) the humoral antibodies in the blood. If the bacilli are held up at the first barrier, there will be evidence of the local resistance in the form of a vesicle or pustule, from which pass red lines indicating the inflammatory reaction in the proximal lymphatic channels, caused by the *toxins*, not the bacilli themselves. If the bacilli pass this barrier but are held up at the second line of defence, namely, the first group of lymphatic glands to which the lymphatic vessels pass, the glands will be enlarged. If the bacilli pass the second line, they reach the blood stream, in small numbers at first, and are distributed widely in the body where, exercising their affinity for lymphatic glands, they affect these mainly, causing a general adenitis; the infection may be overcome by the humoral antibodies in the blood, and the bacilli will reappear in the blood only as temporary showers. If, on the other hand, they overcome the humoral antibodies in the blood, they will cause a septicæmia.

The invasion of the lung parenchyma is also probably a matter of local resistance, as well as of some natural or acquired intrinsic quality in the bacilli themselves, but this appears to the writer to be an incident outside the natural sequence of invasion.

The local lesions are the clinical manifestations of an acute inflammatory reaction, and a rapid passage of the defences indicates a failure of the local resistance. Hence, the local vesicle or pustule is more commonly seen in ambulant cases or in cases of pestis minor, and clinical buboes are usually absent in the severe septicæmic cases, though at post-mortem examination the glands will be found slightly enlarged.

Morbid anatomy.—There is usually a post-mortem rise of temperature and early decomposition; there may be ecchymoses all over the body and submucous hæmorrhages.

The plague toxin has a particular affinity for the endothelial cells of arterioles and lymphatics; in these, it causes degenerative changes which lead to extravasation of blood into the tissues. All the organs are congested, and there are numerous hæmorrhages, in the solid viscera, into the lumina of the hollow viscera, and into serous cavities.

In bubonic and septicæmic plague, the lymphatic glands are enlarged, red and congested, and surrounded by a hæmorrhagic œdema. Histological sections show a hyperplasia, invasion by large numbers of bacilli which are multiplying, small necrotic areas into which hæmorrhage has taken place, and often small abscesses. The spleen is enlarged; it is congested and there are hæmorrhagic foci throughout the organ. The liver is congested; the parenchyma cells show degenerative changes. The kidneys are congested and there may be hæmorrhages into Bowman's capsule; there are often hyalin fibrin thrombi in the Malpighian tufts. There may be hæmorrhages in the brain substance, into the ventricles, or into the sub-arachnoid space. The right side of the heart is dilated, and there may be hæmorrhagic extravasations into the myocardium and a hæmorrhagic pericardial effusion.

In pneumonic cases, there is a hæmorrhagic pleurisy, and the alveoli are filled with a hæmorrhagic exudate. The inflammatory condition extends to the bronchioles, the bronchi, and even the larynx and trachea, and the bronchial lymphatic glands are involved. It is usually a central pneumonia.

The blood picture.—There is never any anæmia except in the chronic suppurative stages of the infection; on the contrary, the great dehydration in the early stages may lead to polycythæmia. A leucocytosis is almost invariable, except in the very severe pneumonic cases when paradoxically it may be absent. The count often rises to 20 to 25 thousand leucocytes per c.mm., or even higher, with an increase in the percentage of lymphocytes, and a decrease in large mononuclears, at first, but later there may be a relative as well as an actual granulocytosis.

In severe septicæmic cases, bacilli may be present in the blood in sufficiently large numbers to make it possible to find them in an ordinary blood smear.

The urine.—This is scanty and highly coloured. It usually contains an appreciable amount of albumin, except in very mild cases. The urea, uric acid and chloride excretion are reduced. A few red blood cells are commonly seen, and there may be obvious hæmaturia.

Suppression of urine may occur in severe cases, when there is much dehydration and a low blood pressure.

SYMPTOMATOLOGY

Clinical types.—These have been foreshadowed in the preceding paragraphs; there are five main clinical types :—

- (i) *The ambulant*, in which there is only a vesicle at the site of invasion with a little local lymphangitis and no constitutional symptoms.
- (ii) *Pestis minor*, in which there is a single gland, or a single group, affected and only mild constitutional symptoms.
- (iii) *Bubonic plague*, in which the local group of glands mainly, but also other glands in different parts of the body, are affected, and there are usually grave constitutional symptoms.
- (iv) *Septicæmic plague*, in which there is an established virulent septicæmia, and usually a rapidly fatal course.
- (v) *Pneumonic plague*.

The so-called cellulo-cutaneous type, which is now relatively rare but from historical records appears to have at one time been the common form, may occur in either the bubonic type, in which the local cellulo-cutaneous lesion corresponds to the bubo, or in the septicæmic type; it is probably more common in the latter.

It should perhaps be emphasized that there is no sharp line of distinction between the bubonic and the septicæmic types; if there is a general adenitis, there must at some time have been a bacillary shower in the blood. In the severe bubonic type, these showers are probably repeated frequently; it is only when the bacillary invasion overcomes, though perhaps only temporarily, the humoral antibodies in the blood that a septicæmia is established.

The first two types need no further description.

Bubonic and Septicæmic Plague

The incubation period is from two to eight days, rarely longer; the average is about four days.

There are sometimes prodromal symptoms for a day or two with malaise, anorexia, apathy, headache and possibly aching pains in the groin, or elsewhere at the site of the subsequent buboes. Usually however the onset is sudden, with a rigor and a temperature rising to

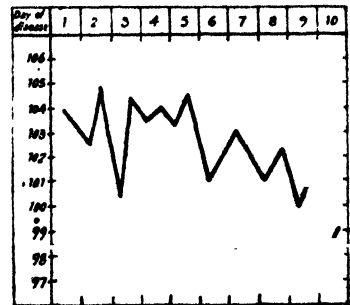


Figure 105 : Temperature chart in a case of bubonic plague.

103° or higher in the first 24 hours, the pulse is rapid and the respirations are increased. There is a severe frontal headache, the mental state is confused, and the speech slurred, there are tremors of the tongue and twitchings of the face muscles, and the gait is very unsteady. There may be severe pains in the back and at the sites of the commencing buboes. The skin is hot and dry, the face bloated, and the conjunctivæ injected. The tongue is swollen and furred; it is very dry and tends to be dark in the centre at first, and then all over (parrot tongue). Vomiting is common. The throat is parched and the patient is very thirsty. The urine is scanty. Prostration becomes extreme within 48 hours of the onset. The temperature may rise higher, and the apathy and dullness change to excitement and eventually sometimes to a maniacal state.

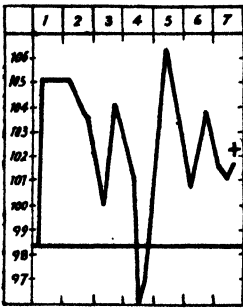


Figure 106 : Temperature chart in a fatal case of septicæmic plague.

The course of the disease.—The temperature continues as a high remittent fever for two to five days and then may fall suddenly, or gradually. The sudden drop is sometimes a prelude to collapse and death, but it does occur in non-fatal cases. In the more favourable cases, the temperature comes down gradually, reaching normal within five or six days. The fall of temperature is usually synchronous with the full development of the buboes, but the temperature may rise again if and when the buboes suppurate.

The buboes.—These begin to appear about the second day. In the severe septicæmic case, they can usually be felt, but death follows before any further development takes place. In the bubonic case, they develop rapidly; they are red, swollen and tender; the discrete glands cannot be felt, as they are matted and

surrounded by oedematous cellular tissue. They are very painful and the patient lies with his knees flexed and/or arms extended to relieve the pressure.

The site of the invasion determines which are the main glands affected; the bare-footed Indian is usually bitten on the toe, so that in India 70 per cent suffer from glands in the groin, with 20 per cent in the axilla, and 10 per cent elsewhere. But this proportion is not maintained in all populations, and in Ecuador, in certain primitive tribes who kill rodents by biting off their heads, the submaxillary group of glands is usually affected (*vide supra*).

In bubonic cases the glands eventually suppurate, and may become secondarily infected.

In septicæmic plague, the lymphatic glands are only slightly enlarged in the fatal cases, but, if the patient recovers, or if death is postponed beyond the usual four or five days, some enlargement may be noticed, and in the former cases suppuration may even occur.

The cellulocutaneous lesions.—These may take the form of carbuncles surrounded by a ring of vesicles which later coalesce, or, at the site of a purpuric patch, the skin becomes moist and necrotic, and the surrounding skin is red and indurated; eventually, the necrotic centre breaks down and an indolent ulcer forms.

Complications.—The commonest complications are associated with the buboes. These may suppurate, point towards the surface, and eventually burst, if they are not opened, or they may involve the underlying vessels and cause profuse and fatal hæmorrhage. When they do burst, they may form chronic sinuses, which become secondarily infected, and the patient may die some weeks later from sepsis, exhaustion, or amyloid disease. Or chronic ulcers may form.

Another complication is septic pneumonia, which will often develop in a debilitated patient with open sinuses; this condition should not be confused with pneumonic plague.

Pneumonic Plague

The onset is usually very sudden and most of the symptoms described above occur, but after 24 hours the patient begins to cough, bringing up a watery sputum which is at first clear, but soon becomes blood-stained, and eventually develops the classical 'prune-juice' colour and consistency. The patient has an anxious expression. There is not usually much pain in the chest, but the patient is cyanotic and some dyspnoea develops early. The physical signs are not characteristic of pneumonia; there is little impairment of percussion note and the vocal resonance is unchanged, but there may be fine râles at the bases.

The heart dullness often extends to the right of the sternum and the heart sounds are feeble. The blood pressure is low. The pulse rate becomes rapid early, increases, and eventually becomes uncountable. Death sometimes occurs within 48 hours from the onset, and it is seldom deferred beyond the fifth day; the condition is always fatal.

Hæmorrhages are frequent; they may take the form of submucous hæmorrhages, purpuric spots, epistaxis, hæmoptysis, hæmatemesis, hæmaturia, and/or melæna.

DIAGNOSIS

Clinical.—A typical case of severe bubonic or septicæmic plague presents a characteristic picture; the sudden onset, high temperature, rapid pulse, great prostration, bloated appearance and conjunctival suffusion, the slurred speech and staggering gait, the apathy and mental confusion, and eventually the buboes, in the former, are not likely to be confused with any other condition, except possibly typhus, if the buboes are late in developing. However, bacteriological confirmation will be desirable.

Bacteriological.—The methods that can be employed are (i) direct examination of a stained smear, (ii) culture, and (iii) animal inoculation.

From the primary vesicle of the **ambulant case**, or the **bubo of pestis minor**, material can be obtained, by gland puncture in the latter case, for direct examination or culture; animal inoculation will usually be unnecessary as the organism will in most instances be uncontaminated by other organisms. In the early stages of **bubonic plague**, the same remark applies, but later when the glands suppurate it will often be necessary to resort to animal inoculation to confirm the diagnosis.

In **septicæmic plague**—and it must be remembered that all bubonic cases are potentially septicæmic—the organism can be obtained from the blood, rarely by direct examination but always by culture and animal inoculation.

In **pneumonic plague**, the plague bacilli are present in large numbers in the sputum; they can be recognized in a direct smear, but it will be advisable to confirm the finding by animal inoculation, whenever possible, as culture will be more difficult on account of contamination.

Outline of technique.—(i) **Smears** should be stained with Gram's stain and methylene or thionin blue. *Pasteurella pestis* is gram-negative and the characteristic bi-polar staining will be easily recognized, but confirmation of the identity of the organism should always be obtained if possible; this is essential where one is dealing with an isolated case.

(ii) To obtain a culture, inoculate blood sugar plates (pH 6.8 to 7.2) and broth tubes with gland juice. Blood from the finger may be inoculated directly on to a plate, or 5 c.cm. from a vein into 100 c.cm. broth flask. The broth and plates should be kept at 22°C., or at room temperature, except in very hot or

cold climates. On the plate, delicate translucent dew-drop colonies appear; these are sticky and can be pushed along the surface of the plate. The broth should show a pure growth.

The certain identification of the culture is complicated by the fact that the plague bacillus is difficult to emulsify, so that serological identification is almost impossible. Animal inoculation is usually considered essential.

(iii) For animal inoculation, it is best to use two white rats and two guinea-pigs. Some of the material should be inoculated subcutaneously into the groin, and some rubbed into a shaved area on the abdomen of one of each species. The latter procedure is important because, if the material is inoculated subcutaneously, the contaminating organisms may kill the animal before the plague infection develops. In a 'positive' case the animals will die of plague septicæmia within 3 to 5 days. (Animals must be kept in insect-proof cages during these tests.)

The animal dying of plague will show general subcutaneous congestion and a fibrinous exudate in the peritoneum; and locally necrosis of the tissues, hæmorrhagic œdema, and the lymphatic glands enlarged and buried in hæmorrhagic œdema. At the site of the percutaneous inoculation, *i.e.* the shaved area, there may be umbilicated pustules. In the guinea-pig, miliary necrotic nodules will be seen on the surface and throughout all the organs. Pure cultures of plague bacilli will be obtainable from most of these sites.

For the identification of the cultures of *Pasteurella pestis*, 0.1 c.cm. of a 24-hour broth culture should be inoculated intraperitoneally; the animal will die in two or three days.

The agglutination test.—This test is of no value in the diagnosis of plague for the reason stated above, namely, the difficulty of obtaining a bacillary emulsion, because the agglutinins appear late, the titre is low, and bacteriological diagnosis is relatively easy.

Differential diagnosis.—One has to consider any febrile condition either severe or mild, and the various venereal buboes, *e.g.* syphilis and lymphopathia venereum, other causes of local, *e.g.* sepsis, and general lymphadenitis, *e.g.* glandular fever; it will not be possible to review these in detail here.

As mentioned above, a septicæmic or a severe attack before the buboes develop may be mistaken for typhus, and of course any other severe toxæmic condition; the typhus rash should be looked for, but it appears too late to be of any real value.

PREVENTION

Prevention has to be considered under two main headings :—

(A) *The prevention of the introduction of plague into a non-endemic area.*

(B) *The control of plague in an endemic area.*

The reader is referred back to p. 328, where the transmission cycle is discussed.

A. The prevention of the introduction of plague into a non-endemic area.—The essentials for plague to occur are, shortly, the plague bacillus, the flea vector, the rodent reservoir, and susceptible man living in a suitable environment. Except the plague bacillus, in most countries the other essentials are present and suitable, to a greater or lesser degree, for plague to occur; the introduction of the plague bacillus would be likely to start an outbreak. The bacillus may be introduced in its rodent reservoir or in a flea vector. Theoretically, it could also be introduced in an infected man, but this is probably a negligible danger.

It would lead to much duplication to discuss the preventive measures under the two headings separately. All the measures that are used to control plague in an endemic area could be applied in a potentially endemic area, as safeguards in the event of the introduction of the bacillus, but how far it will be profitable to employ them will depend on the extent of the danger, and this will depend on the proximity of an endemic area and on

other factors. For example, it will always be worth controlling the rats in dock areas in any country, but on the other hand prophylactic inoculation of the population where plague has not yet occurred would be a waste of energy.

References will be made in appropriate places to the prevention of rat and flea migration, for it will be mostly in the endemic areas themselves that the measures to prevent introduction of infection into new countries will have to be made.

B. The control of plague in an endemic area.—If this cycle can be broken at any point, plague will not occur; if it can be weakened, plague will be reduced.

In pneumonic plague, the infection is passed from man to man (*see figure 102, p. 328, right-hand cycle*); isolation of the sick is therefore essential to protect the general population; doctors, attendants, and nurses must be protected from droplet infection by masks and other measures; and the community as a whole should be protected against the effects of infection, by prophylactic inoculation.

In the transmission of bubonic plague, man does not constitute an essential link (*see figure 102, middle cycle*) and, in an outbreak, infected man is an almost negligible factor as a reservoir of infection, for the reasons that the septicæmia seldom reaches the degree necessary for transmission, and that his fleas are poor transmitters. Isolation and treatment of the sick alone will therefore achieve nothing in the way of checking an outbreak of bubonic plague, though the possibility of the development of pneumonic plague during a bubonic plague outbreak will make such a measure a reasonable precaution.

If, however, the rodent–flea–rodent cycle is broken, by attacking the rodent–flea or the rodent, or both, the epizootic will cease and the sporadic infection of man will no longer occur.

If it is not possible to break the epizootic, man can to some extent be protected from infection by excluding rats from his habitations and protecting his person from the bites of rat–fleas.

Finally, man can be protected from the effects of infection by increasing his immunity by inoculation.

Prevention must therefore be considered under the following headings:—

1. *Isolation and treatment of the sick.*
2. *Measures against rats or other rodents.*
3. *Measures against fleas.*
4. *Protection of man from rats and fleas.*
5. *Prophylactic inoculation.*

1. **Isolation and treatment of the sick.**—There is little more that need be said here under this heading, except it must be remembered that it is mainly against droplet infection in pneumonic plague that protection has to be given to attendants, so that the hospital rooms should be light and airy and wherever possible some form of screen protection should be provided for the personnel.

2. **Measures against rats or other rodents.**—These measures will constitute insurance against plague infection in any country, but they are naturally more important in an endemic area, and they must be intensified in the presence of an outbreak or when an outbreak is threatened.

A plague epizootic amongst the local rat population, or a high infection rate amongst fleas, is the danger signal, and an efficient public health department will, so to speak, keep its finger on the pulse of the rat and flea populations, so that where and when conditions are most favourable for an outbreak the measures may be concentrated.

A large number of deaths amongst rats, or of 'rat falls' as they are called, is a warning signal that has been known to the inhabitants of plague-infected countries for a thousand years, and the modern health officer should aim at getting his information ahead of this.

The rodent factors that determine incidence (*see* p. 329) are susceptibility and immunity, habits, and density of population. The former two are dependent largely on species, and though it is true that the natural replacement of one species by another has probably influenced the incidence of plague, it will not be possible to do this artificially, so that measures against rats amount to the reduction of rat population and the prevention of rat migration.

Rats will only multiply as long as they are provided with harbourage and food, and the construction of rat-proof buildings and particularly rat-proof grain stores is an important measure of prevention of plague. Other general measures include the proper disposal of refuse, the provision of covered receptacles for household garbage, and the rat-proofing of the sewage system.

The domestic cat is a valuable assistant in keeping down the rat population in warehouses, ships, etc.

Rat destruction will of course form an important part of the programme. There are many methods; these include trapping, poisoning, infecting with Danysz virus, and gassing. The last-named is by far the most effective.

There are many forms of **rat trap**; some kill the rats, others capture them alive. It should be remembered that the fleas leave a dead rat; therefore during a plague epizootic it is advisable to use traps which keep the rats alive or which destroy the fleas as well. Rats must then be killed in such a way that their fleas are also killed, or the body should be immediately plunged into strong phenyl or other disinfectant. The dead rat is a grave danger and should be handled only by specially protected personnel.

If the rat-flea population is to be investigated, it will also be necessary to capture the rats alive. They are then chloroformed or placed in a gas chamber; this will kill the fleas also. The fleas are then combed out, counted, and identified.

There are innumerable **rat poisons**. These again should not be used during an epizootic. Many of them are dangerous to cattle and other animals, and are therefore of limited use. Barium carbonate is however a useful poison because one to two grains will kill a rat, which usually goes into the open—in search of water—to die, whereas dogs can take up to 100 grains and cats and chickens from 10 to 15 grains without harm. Small pellets of a mixture of three parts of barium carbonate and four parts of dough are made, and are left in suitable places. It will be as well to vary the excipient, and tallow is also a useful one.

Gassing has to be carried out by trained squads, but it is by far the most effective. Some form of cyanogen gas is the best, as it kills both rats and fleas. In ships, it is introduced by an elaborate system of tubes which are carried to all the corners of the holds of ships, and then gas is fed from a central cylinder or generator where it is produced by the action of acid on potassium cyanide. After sufficient time has elapsed, the gas is drawn out again or blown out by pumping in air; there is danger from pockets of gas remaining in the holds. The gas is sometimes mixed with some pungent gas that acts as a warning of the presence of the scentless hydrocyanic acid gas. Half an ounce of potassium cyanide will produce enough gas to fumigate 100 cubic feet of hold, or warehouse.

For rat burrows, an easier way is to apply the cyanogen gas in the form of a powder from which the gas is given off either slowly or rapidly.

Cymag is such a powder made by Imperial Chemical Industries. It contains 20 per cent hydrocyanic acid, and the gas is given off slowly. Another form is 'calcid brickettes' which are ground up into a powder and blown into the holes. In these cases, all the holes must be effectively blocked up before the gas or powder is pumped in, or the rats escape; this applies particularly to the powders that give off the gas slowly.

In India, the *neem-batti*, which can be made locally with the addition of simple chemicals, is used widely. Potassium chlorate—grains 120, potassium nitrate—grains 90, and sulphur—grains 120, powdered and mixed with 5 drachms of mustard oil are made into a paste; to this a drachm of pepper and a handful of neem leaves are added; this is rolled into the form of a candle, and a cloth wick that has been dipped in saturated potassium chlorate solution and dried is attached. The whole candle is dried thoroughly. For use the wick is lighted and the *batti* is then thrust into a rat hole and the hole closed behind it. The *neem-batti* gives off sulphur dioxide which kills rats, but it not so effective against fleas.

The measure to be adopted against other rodents will naturally depend on the rodent concerned.

In the United States a very elaborate system of investigation of wild rodents and their fleas is in operation, so that, as in the case of rats, the danger may be met when and where it arises. It is probably this vigilance that has kept the country free from plague in the past (*vide supra*).

Protection of ships against rats.—Inter-country movements of rats is almost entirely on ships, and international quarantine regulations are rightly aimed mainly at the 'deratization' of ships. The effect of such regulations is shown in the fact that the U. S. Public Health Service report that, whereas 50 per cent of ships arriving at Atlantic ports were rat-infested between 1925 and 1927, the percentage had dropped to 8.4 per cent in 1937.

The danger is from shore-rats going on board at the infected ports, and ship-rats going ashore at uninfected ports. Therefore, ships lying alongside in plague-infested ports should be at least four feet from the dock, all hawsers should be provided with efficient rat-guards, *i.e.* metal discs at least three feet in diameter, properly adjusted, *i.e.* fixed at right-angles to the hawsers, and all gangways should be protected by a band of fresh tar and should be raised at night when not in use.

3. **Measures against fleas.**—Most of the gassing measures are as effective against fleas as against rats, and there are few measures that are designed to destroy fleas independently of their rat hosts; as suggested above, care should be taken, when rats are killed, that their fleas perish with them, and both trap and rat should be placed in disinfectant.

The floors and particularly the corners of rooms where rats have been found should be pyrethrum sprayed; the strength used for mosquitoes (*q.v.*), namely, a one-in-twenty dilution in kerosene of the usual concentrated pyrethrum extract, will be suitable.

Clothes and bedding that are suspected of harbouring fleas can also be sprayed with this.

Fleas are likely to be carried from place to place and country to country in grain bags, cotton and jute bails, gunny rolls, etc., and suitable disinfection of any such material coming from an active endemic area should be carried out.

4. **Protection of man from rats and fleas.**—The building of rat-proof houses is much easier than the rat-proofing of existing houses. The main points in a rat-proof house are that the lower walls and floors should be of hard brick and concrete, respectively, and that the former should

sink at least two feet into the ground to prevent rats burrowing under it. All ventilators and drains must be protected by iron gratings.

During a plague epidemic, evacuation of all infected houses, as indicated by 'rat falls' as well as by human cases, is an important measure. The occupants should not return for several months, and then only when the house has been shown to be plague-free by placing caged guinea-pigs in the house for several nights; if they survive, the house is probably free from infection.

For those working in a plague-infected area and especially those employed on plague duty, the clothing should be carefully selected. White is preferable, as fleas can be seen easily and picked off. Fleas can, but do not, as a rule, bite through clothes. The clothes should be such that fleas cannot get inside them; therefore, trousers and shorts are unsuitable and should be replaced by knee breeches or 'jodhpurs', gum-boots give good protection but the tops should be closed; the sleeves must be tightly bound round the wrists and those handling rats must wear leather or rubber gloves; and an open neck is also a danger, as fleas may fall from the roof.

5. Prophylactic inoculation.—

Historical.—Haffkine introduced the inoculation against plague at the end of the last century, during the last great pandemic. This was the first occasion on which a vaccine had been used on a large scale as a public health measure. He used a six-weeks-old heat-killed (65°C. for one hour) culture of *Past. pestis* in broth to which 0.5 per cent phenol had been added and gave 4 c.cm. to an adult. Figures collected by the Plague Commission suggested that this inoculation caused an 80 per cent reduction in the infection rate and an 80 per cent reduction in mortality amongst those infected. Since this date, many millions of doses of this vaccine have been given in India and elsewhere, but the statistical value of some of the data that was collected by the Plague Commission and later has been questioned.

In 1907, Strong, working in the Philippines, used a live avirulent strain of plague as a vaccine, but this vaccine did not come into general use until 1935, when de Vogel and Otten re-introduced vaccination with an avirulent living culture of plague; it has been reported that the immunity produced by this live strain is much higher than that produced by a dead virulent culture. This live avirulent strain has now been used in Java for some years and over two million doses given without ill-effects.

Although it is not yet finally settled which is the more effective, the modified Haffkine vaccine now used in India, or the live avirulent vaccine of Otten now used exclusively in Java, Madagascar, and elsewhere, at present the indications outside India are all in favour of the latter, whilst in India the policy at present is to trust a well-tried friend. This policy has been influenced by the fact that avirulent live vaccines tend to deteriorate rapidly, so that there would be great difficulties in the way of maintaining stocks, and distributing the vaccine in India.

Certain modifications in the original Haffkine vaccine have been made, e.g. it is now grown for 48 hours at 37°C. on agar, and a saline suspension is made; this is killed by heating at 54°C. for 15 minutes; 0.5 per cent phenol is added, and it is standardized to contain 1,000 million organisms per c.cm. The antigenic properties of this vaccine have been shown to be much higher than those of the old vaccine; mice are used for these tests.

The vaccine is best given in two doses, 0.5 c.cm. for the first dose and 1.0 c.cm. a week later. The reactions produced by the earlier vaccines were very severe, but with the modern vaccine they are less, though still more severe than with most vaccines. The vaccine provides protection for six to eight months.

TREATMENT

Good nursing will play a very important part in determining the recovery of the patient. He should be confined strictly to bed and not be allowed to do anything for himself; he will want plenty of fluid, possibly drip-feed intravenous glucose, and frequent fomentations to the buboes. Further, such possible emergencies as hæmorrhage from septic erosion of large vessels may have to be met.

The treatment may be considered under the headings, (a) *symptomatic*, (b) *local*, and (c) *specific*.

A. Symptomatic treatment.—The treatment is that for any asthenic febrile disease; for hyperpyrexia, hydrotherapy should be employed, and antipyretic and depressant drugs avoided; the diet should be fluid but nourishing, but since the disease is a short one, it is not necessary to force the calories though the patient should be encouraged to drink freely, imperial drink, barley water, or glucose water. Intravenous glucose, 5 per cent, can be given fairly rapidly if there is a lowered blood pressure, but otherwise by the drip-feed method almost continuously.

For the generalized pain and restlessness, phenobarbitone should first be tried, and if this fails, morphia may be given judiciously. Digitalis and strophanthus are recommended as a routine prescription; caffeine is a useful stimulant and probably better than alcohol in this condition. Collapse should be met by intravenous therapy and subcutaneous ether, camphor in oil, or cardiazol.

B. Local treatment.—The buboes may play an important part in the symptomatology, and they may require vigorous local treatment. The fever is likely to remain high until the buboes develop, and these may cause a secondary rise when they suppurate. There was an old teaching that it was good practice to relieve the tension by opening the buboes early to prevent the infection disseminating; such a procedure was entirely opposed to modern surgical teaching, and was much more likely to cause a septicæmia, which in fact it often did, than to prevent it.

In the early stages, the buboes may be painted with liniment of iodine, or, if they are very painful, with glycerine and belladonna, fomented frequently, or the infra-red lamp applied to them. On no account should the buboes be opened until they are definitely pointing, when it will be permissible to put in a scalpel to relieve the pressure and pain. When they are opened, they should be allowed to drain, sulphonamide or sulphapyridine powder should be put on, and a dry dressing applied, or, if there is any surrounding inflammation, hot fomentations might be continued. Sulphapyridine in full therapeutic doses by mouth at this stage is also useful. If these sinuses are allowed to become secondarily infected, the course of the disease may be prolonged for weeks or even months.

C. Specific treatment.—The present indications are that serum treatment is likely to be replaced entirely by chemotherapy in the near future.

Serum treatment.—Yersin's serum has no direct action on the pasteurella infection; nor is it antitoxic, but is described as 'anti-infections' (Strong, 1942), that is, it prevents the establishment of infection in an infected person, and therefore it must be given early. Even after excluding a group of cases for various reasons, a procedure which is always open to suspicion, it has seldom been possible to show more than about a 10 per cent improvement in death rate, e.g. from 74 per cent in 200 controls to 63.5 per cent in serum-treated cases. Recently, Sokhey (1936) has produced an anti-serum which has proved more efficacious, and in several series the death rate has been of the order of 25 per cent, with the control series showing about a 50 per cent death rate.

The initial dose recommended is usually for 50 to 100 c.cm., and this must be repeated daily until the temperature is normal.

Chemotherapy.—Prior to the introduction of the sulphonamide drugs, many drugs had been tried without any conspicuous successes, *e.g.* intra-venous iodine, mercurochrome, germanin.

Schütze (1939) demonstrated the efficacy of sulphapyridine in plague-infected rats and mice, and Wagle *et al.* (1941) obtained good results in human plague with both sulphapyridine and sulphathiazole; their death rates were 52 per cent in controls, 28 per cent in serum-treated patients, 24 per cent with sulphapyridine, and 15 per cent with sulphathiazole.

These workers gave 1 gramme *statim* and 0.5 gramme four-hourly; it is possible that better results might have been obtained with full therapeutic doses, and there is an obvious possibility that some of the newer compounds, *e.g.* sulphadiazine, may prove more efficacious.

PROGNOSIS

This of course will depend on treatment to a large extent.

The pneumonic form is always fatal.

In published series of treated cases, the control series always have death rates between 50 and 75 per cent. In such series, ambulant cases and cases of pestis minor will probably not be included, so that the gross death rate is probably less.

The prospects of the patient depend on his resistance, and can be measured by the degree of septicæmia from which he suffers. In cases with uncontrolled septicæmia and large numbers of bacilli in the blood, the death rate is probably 100 per cent, but, in bubonic cases with only bacillary 'showers', it is between 25 and 50 per cent.

In the bacillæmic case, the patient usually dies within the first five days. However, the prognosis should always be guarded, as recovery sometimes takes place in the most desperate cases, whereas a patient who appears to be getting on well may suddenly fall back dead.

Death may take place after several weeks from septic complications.

REFERENCES

- BACOT, A. W., and MARTIN, C. J. Observations on the Mechanism of the Transmission of Plague by Fleas. *J. Hyg., Plague Supp.*, III, 423.
- GAUTHIER, J. C., and RAYBAUD, A. Sur le rôle des Parasites du Rat dans la Transmission de la Peste bubonique. *Compt. Rend. Hebd. Soc. Biol.*, 54, 1497.
- GEORGE, P. V., and WEBSTER, W. J. Plague Inquiry in the Cumbum Valley, South India. *Indian J. Med. Res.*, 22, 77.
- HAMPTON, B. C. (1940) Plague in the United States. *Pub. Health Rep.*, 55, 1143.
- LOWE, J. (1942) Note on the Work of Dr. P. L. Simond on the Transmission and Epidemiology of Plague. *Indian Med. Gaz.*, 77, 418.
- NUTTALL, G. H. F. (1899) On the Rôle of Insects, Arachnids and Myriapods, as Carriers in the Spread of Bacterial and Parasitic Diseases of Man and Animals. A Critical and Historical Study. *Johns Hopkins Hosp. Rep.*, 3, 154.
- OGATA, M. (1897) Ueber die Pestepidemie in Formosa. *Centralbl. Bakt.*, 21, 769.
- OPTEN, L. (1935) Pest-vaccinatie op Java. *Geneesk. Tijdschr. Nederl.-Indie*, 75, 1850. (Abstract—*Trop. Dis. Bull.*, 1936, 33, 365.)
- ROGERS, L. (1933) Notes on Making Epidemic Forecasts. *Indian Med. Gaz.*, 68, 125.
- SCHUTZE, H. (1939) Chemotherapy in Plague Infection. *Lancet*, i, 266.

- SIMOND, P. L. (1898) La Propagation de la Peste. *Ann. Inst. Pasteur*, **12**, 625.
- SOKHEY, S. S. (1936) Un Nouveau Sérum Antipesteux. *Bull. Office Internat. Hyg. Pub.*, **23**, 1097.
- STRONG, R. P. (1907) Studies in Plague Immunity. *Philippine J. Sci.*, **2**, 155.
- Idem* (1942) Plague. *Stitt's Tropical Diseases*, **1**, 651. H. K. Lewis and Co., Ltd., London.
- DE VOGEL, W. (1935) Vaccinations antipesteuses avec un virus vivant aux Indes Néerlandaises. *Bull. Office Internat. Hyg. Pub.*, **27**, 1542. (Abstract—*Trop. Dis. Bull.*, 1936, **33**, 364.)
- WAGLE, P. M., SOKHEY, S. S., Chemotherapy in Plague. *Indian Med. Gaz.*,
 DIKSHIT, B. B., and GANAPATHY, **76**, 29.
 K. (1941).

TULARÆMIA

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Definition.—Tularæmia is an acute febrile disease of moderate severity, with a tendency to pneumonic complications, caused by *Bacterium tularensæ*, which is transmitted to man from rabbits and other wild-life in many ways—for example, by the bite of insects, such as *Chrysops discalis*, and by direct contact with infected animals—and which usually causes a primary lesion at the point of entry.

Historical.—*Bacterium tularensæ* was first encountered as a plague-like infection in a ground-squirrel in Tulare country, California, by G. W. McCoy in 1911, and was later identified as the causal organism of 'deer-fly fever' in man in the state of Utah. The disease was given the name 'tularæmia' by Francis in 1921.

ÆTIOLOGY

The causal organism.—*Bacterium tularensis* (or *Brucella tularensis*) is a very small gram-negative cocco-bacillus, 0.2 to 0.7 μ by 0.2 μ ; in specimens stained with weak carbol-fuchsin or aniline gentian violet, it is surrounded by a clear area that probably represents a capsule. It grows on glucose blood agar to which a piece of rabbit's spleen has been added. It is killed by heat (60°C. for 10 minutes), but survives drying, and possibly for this reason it is readily transmitted to laboratory workers.

Pathogenicity in animals.—While some 24 small wild animals have been found infected in nature, a number of others, as well as birds, have been shown to be susceptible. Most laboratory animals are very susceptible, but the guinea-pig is the most satisfactory experimental animal and the rat the least. The guinea-pig dies with a generalized infection three to five days after inoculation, and shows lesions similar to those caused by plague. Attenuated cultures however may produce a non-fatal infection.

TRANSMISSION

Sources of infection.—Up to 1940, twenty-four species of wild-life had been found infected in nature, but wild rabbits and hares are by far the most important source, and 90 per cent of the cases occurring in the United States can be traced directly or indirectly to these animals.

Agents of transmission.—There is no disease that has such a variety of modes of transmission as tularæmia; it may be transmitted to man by contaminated drinking water, or by his eating under-cooked infected animals; it is known to be transmitted to man by a variety of blood-sucking insects, including *Chrysops discalis*, *Dermacentor andersoni*, *variabilis* and *occidentalis*, and *Hæmaphysalis leporis-palustris*; others, including mosquitoes, have been suspected; and it is perhaps most commonly transmitted directly by the handling of infected animals and birds. In the transmission from animal to animal, innumerable animal parasites are involved.

Route of entry.—The organism may enter through the skin, at the site of an abrasion or possibly through the intact skin, through external mucous membranes, e.g. the conjunctiva, *via* the intestinal tract, and possibly *via* the respiratory tract, or it may be injected into the deeper layers of the skin by a biting insect.

Immunity.—There is evidence that immunity is complete and lifelong. No true second attack has been reported.

Agglutinins appear usually in the second week, but their appearance may be delayed until the third week. A titre of 1 in 80 is considered diagnostic, but the titre may rise to 1 in 5,000; agglutinins usually persist for many years, if not for life, and in one case they are believed to have persisted for 33 years (Foshay, 1940). There is some slight degree of cross immunity with (other) brucella, but none with pasteurella infections.

An anti-serum has been produced, but its therapeutic efficacy seems questionable. On the other hand, some definite immunity appears to be conferred by vaccination with killed cultures.

EPIDEMIOLOGY

Geographical distribution.—All the earlier studies of this disease were conducted in the United States and it has now been reported from every state in the Union. It has also been reported from Japan (1925), Russia (1926),



Figure 107 :
Chrysops
discalis.

Norway (1929), Canada (1930), Sweden (1931), Austria (1935), and more recently from Turkey, Asia Minor, and North Africa.

The disease can lay little claim to being tropical, but, as it has certain features common to many tropical diseases, especially in regard to its ætiology, a short description of it is included in this book. The disease is probably more widespread than our present information on this subject indicates, and with the dissemination of the knowledge of the clinical picture, of the methods of diagnosis, and of the various modes of transmission, amongst medical men in other countries, it seems very probable that it will be found to have a much wider distribution.

Epidemic features.—The disease may appear in epidemic form when a water-supply is contaminated, when a number of persons take an infected meal, or when, in special circumstances, they are subjected to bites by infected insects; such an incident occurred in Utah when 30 boys in a camp of 170 were infected by the bites of *Chrysops discalis* on their uncovered backs. Nevertheless, tularemia is essentially a sporadic disease; it is doubtful if the infection is ever transmitted from man to man, directly or indirectly.

Seasonal incidence.—Man may be infected at any time of the year, and the season of incidence will depend on the mode of infection. This is very well illustrated in figure 108 which shows the season of incidence in 347

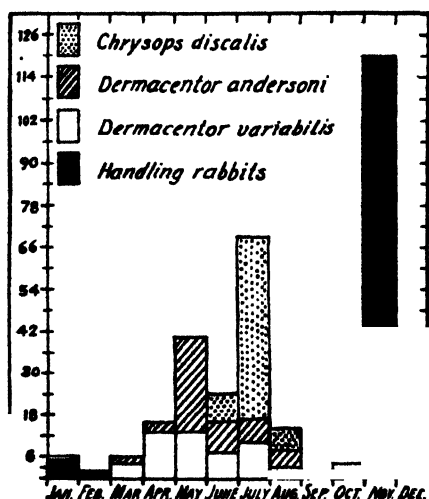


Figure 108 : Chart showing seasonal distribution of 347 cases of tularemia infected by different methods, occurring in the United States in a period of 12 years ending 31st December, 1935 (from data supplied by Francis, 1937).

cases occurring, over a period of 12 years, in the United States, arranged according to their probable mode of infection. Transmission by the dog tick, *Dermacentor variabilis*, occurs in nearly any month in the year, but mostly in the spring; transmission by *Dermacentor andersoni*, the wood tick, occurs during the late spring and summer when the insects are most active; transmission by *Chrysops discalis* is confined strictly to the summer months with a marked peak in July; and transmission from the handling of dead rabbits is essentially a winter incident.

Age, sex, and occupational incidences.—These again are entirely dependent on the mode of infection. Hunters and campers, housewives, butchers, and laboratory workers are amongst those most commonly infected.

PATHOLOGY

The organism first produces a local lesion at the site of entry, but there is rapid generalization of the infection, *via* the lymphatics and blood stream; if the patient's natural resistance is high, only a temporary bacillæmia occurs, otherwise a septicæmia.

The proximal lymphatic glands are first infected, and later there may be a generalized lymphadenitis; the lymph nodes become inflamed and may eventually break down and form abscesses.

Post-mortem, small necrotic foci are found in the spleen, both under the capsule and in the parenchyma, in the liver, and in the lungs.

In the primary pneumonic infections, there is a pneumonitis, usually involving at least one whole lobe, without the necrotic foci; the pleura is nearly always involved and there is a pleural effusion.

Histopathologically, the local lesion shows a necrotic centre surrounded by an area of polymorphonuclear infiltration, outside which there is some lymphocytic infiltration of the surrounding tissues. A similar change occurs in the affected organs; in the lungs, outside the necrotic focus there is a zone of alveolar exudate, and the inflammatory changes may involve a whole lobe and the pleura; and in the liver occur degenerative changes of the parenchyma cells followed by necrosis.

More chronic lesions which resemble tuberculosis are sometimes observed. The necrotic centre is surrounded by an area of epithelioid cells and fibroblasts, outside which is a zone of lymphocytic infiltration; scanty giant cells may be found in these lesions.

Blood picture.—A moderate leucopenia is the rule, and even in the pneumonic cases the leucocyte count is seldom above 10,000 c.mm.

SYMPTOMATOLOGY

Clinical types.—The usual classification refers to the ulcero-glandular, oculo-glandular, glandular and typhoid types, but this classification is neither satisfactory nor comprehensive. In our probably incomplete state of knowledge regarding the scope of *Bact. tularensis* infection, it will be unwise to adopt any fixed classification, for, as our experience of this disease widens, a satisfactory one will probably evolve.

The clinical picture shows considerable variation according to the mode of entry of the causal organisms. The most typical symptomatology, and the one that is described below, occurs in those cases in which infection enters through the skin, either through an abrasion or by the agency of an insect, causing a local ulcer and local glandular infection. If it enters through the conjunctiva, this structure is first involved and the clinical picture is that of the so-called oculo-glandular type; generally in this type of infection the disease is more severe. However, in either of these cases the local reaction may be slight, and the infection may by-pass the local glands, causing a bacillæmia which may be associated with general glandular enlargement, or a septicæmia, and produce an attack of the so-called 'typhoid type'. This latter is also the form that the disease usually takes when the infection is acquired by eating insufficiently-cooked infected rabbits.

Cases have been reported in which meningeal symptoms developed early and the meninges were shown to be infected with *Bact. tularensis*.

Finally, there is the clinical type in which pneumonia is a primary manifestation, as distinct from the pneumonia which may develop as a complication in any severe form of tularæmia. On analogy with plague, and from suggestive epidemiological reports, it seems possible that in some of these cases there is a primary infection of the lung.

The clinical course.—The incubation period is in the large majority of cases from three to four days; the extremes are 24 hours and ten days. The onset is sudden with general symptoms, headache, fever with chilliness, vomiting, prostration, and pains all over the body, very suggestive of influenza or a sub-typical dengue. The next day, or sometimes earlier, attention is drawn to the local lesion which now develops into an ulcer, and the proximal lymph nodes become enlarged and painful. The fever rises sharply, often reaching 104°F. in 24 hours; after two or three days the temperature falls to the 100° line, or even to normal for one to three days, and then relapses as a high continued or remittent fever (see figure 109), accompanied by fairly profuse sweating, loss of weight and increasing

debility, usually for three weeks, even in an uncomplicated case; the convalescence is very prolonged, lasting from two to three months.

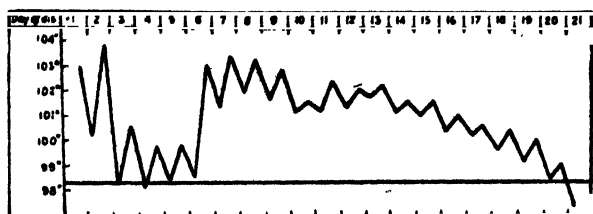


Figure 109 : Characteristic chart of uncomplicated tularæmia.

The glandular enlargement may persist throughout convalescence, or at an early date the glands may become necrotic, suppurate, point, and eventually break through the skin leaving a sinus that may not heal for many months. Subcutaneous nodules may form along the

course of the infected lymph channels; these persist as hard tender movable lumps for some months and occasionally they break down.

A rash is sometimes reported, but it is not constant, nor characteristic, either in its time of appearance or form.

The spleen may be slightly enlarged.

In the primary **pneumonic form**, the onset is usually with a cough, pleuritic pain, headache, general malaise, and a sharp fever usually with chills. The temperature continues as a high remittent fever (see figure 110) with periodic chills. The physical signs are sometimes atypical, and the pleural effusion masks the x-ray picture, so that the diagnosis is frequently postponed until the autopsy. Milder examples of this type are probably very frequently missed, but, judging from the reported cases, one must consider the prognosis very bad.

Complications.—The commonest are those associated with the local lesions and the glandular infections; ulcers and the sinuses that result from suppurating glands may become secondarily infected and persist for months. The local eye lesions may lead to the loss of an eye.

Of the more severe complications, pleurisy and pneumonia are the most frequent; in fact, pneumonia is such a common complication that it might almost be considered a special form of the disease, and there is a tendency in the literature to include it in the classification of the types of the disease (*vide supra*).

DIAGNOSIS

The circumstance may lead one to suspect that a febrile illness is tularæmia, when for example the patient has been bitten by *Chrysops discalis* in an endemic area during the transmitting season, when he has been on a shooting expedition, killing, skinning and/or cleaning rabbits, or when he has been in contact with *Bact. tularensis* in the laboratory. On the other hand, many cases have occurred in which the mode of infection was completely obscure.

Clinically, the combination of a local lesion, or conjunctivitis, with tenderness and enlargement of the lymphatic glands, shortly after a febrile influenza-like attack that showed an initial sharp rise, a temporary remission, and a further febrile bout of about a fortnight's duration ending by lysis, should arouse suspicion.

The pneumonic type will be particularly hard to diagnose clinically, except that it is a slightly atypical pneumonia with pleurisy, which does not respond to the usual chemotherapeutic agents or to serum.



Figure 110 : fatal case of pneumonic tularæmia (Kennedy, 1942).

Bacteriological evidence is of course the most desirable, but is not at all easy to obtain. On media inoculated with the blood or gland juice, growth has been obtained, but not readily, and animal inoculation is the surest method. Two to five cubic centimetres of defibrinated blood diluted with an equal amount of normal saline inoculated intraperitoneally into a guinea-pig will produce an infection that will kill the animal within three or four days, with the production of the typical lesions from which *Bact. tularensis* can be recovered.

A diagnosis may be made by the **agglutination test**, but this will mostly be in retrospect, for the titre often only reaches 1 in 80 by the third or fourth week, though it may eventually rise to 1 in 5,000 in convalescence. The titre falls slowly, and agglutinins have been reported to persist up to 33 years. Sometimes the sera will also agglutinate *Br. melitensis* and/or *abortus* (*vide supra*).

An **intra-dermal test**, in which 0.05 c.cm. of a bacterial suspension produces a weal five millimetres in diameter in a positive case, has had a few advocates; it gives a positive result at an earlier date, but it is probably less specific than the agglutination test.

PREVENTION

A study of the methods of infection will immediately indicate a number of ways in which the dangers of infection can be obviated, or at least reduced (*vide supra*).

As there is considerable danger of laboratory infection, very special precautions should be taken with regard to the handling and isolation of inoculated animals, *e.g.* rubber gloves should always be used.

Prophylactic inoculation has not proved entirely satisfactory hitherto, but recently Foshay *et al.* (1942) have shown that some protection is given by inoculation with dead cultures, and that infections in inoculated persons are milder.

TREATMENT

No really successful specific has yet been found. Serum treatment has been used extensively, and the results of treatment in 600 cases with a similar number of controls have been reported (Foshay, 1938). The results were not very striking; the death rate was 4.2 per cent in the treated cases, but Foshay considered that they demonstrated the value of the serum.

Otherwise, the treatment is symptomatic. Surgical interference with the enlarged glands or the nodules is not to be recommended; open local lesions should be treated with hot saturated magnesium sulphate compresses.

PROGNOSIS

During 1938 and 1939, there were about 4,300 cases reported in the United States, with a death roll of about 290, a rate of approximately 6.7 per cent.

From the point of view of invalidism, it is a serious disease, as full health is seldom restored under 3 to 4 months, and the average period of hospitalization is often reported as over 100 days. In some cases, chronic sinuses have persisted for two years.

The cases in which infection was conveyed by eating under-cooked rabbits seem to be more serious, and a 60 per cent death rate is reported in one such series.

Pulmonary complications cause deterioration in the prognosis; it is reported that 30 to 40 per cent of patients with these complications die, and more than half the patients who die are in this group. The death

rate amongst patients with primary lung infections appears to be even higher. Those in which meningitis occurs always die.

REFERENCES

- FRANCIS, E. (1921) The Occurrence of Tularemia in Nature as a Disease of Man. *Pub. Health Rep.*, **36**, 1731.
- Idem* (1937) Sources of Infection and Seasonal Incidence of Tularemia in Man. *Pub. Health Rep.*, **52**, 103.
- FOSHAY, L. (1938) Effects of Serum Treatment in 600 Cases of Acute Tularemia. *J. Amer. Med. Assoc.*, **110**, 603.
- Idem* (1940) Tularemia: A Summary of Certain Aspects of the Disease including Methods for Early Diagnosis and the Results of Serum Treatment in Six Hundred Patients. *Medicine*, **19**, 1.
- FOSHAY, L., HESSELBROCK, W. H., WITTENBERG, H. J., and RODENBERG, A. H. (1942). Vaccine Prophylaxis against Tularemia in Man. *Amer. J. Pub. Health*, **32**, 1131.
- KENNEDY, J. A. (1942) Pulmonary Tularemia. *J. Amer. Med. Assoc.*, **118**, 781.
- McCoy, G. W. (1911) A Plague-like Disease of Rodents. *Pub. Health Bull.*, No. 43. United States Treasury Department, Washington.

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Definition.—The undulant fevers, or brucelloses, are a group of diseases, characterized by long-continued fever which sometimes adopts an undulant periodicity, caused by bacteria of the genus *Brucella* and transmitted to man from animals by various means.

Historical.—The earliest attempt to separate the first recognized form of this disease from other long-continued fevers was made by Marston in 1861; he described a disease that occurred in British troops in Malta. David Bruce isolated the causal organism in 1887. In 1897, Hughes wrote an important monograph on the subject and suggested the name undulant fever; it was however at this time generally known as Malta or Mediterranean fever. In 1904, the Mediterranean Fever Commission was sent out under the auspices of the British Government to investigate the means of spread of the disease; they discovered that goats were the reservoir of infection and that the disease was spread mainly by the agency of goat's milk.

Contagious abortion was recognized as a disease of cattle early in the 19th century in Great Britain. In 1897, Bang isolated the causal organism of this cattle disease, and, in 1914, Traum isolated a similar organism from pigs. In 1918, Alice Evans demonstrated the close antigenic relation between the causal organism of Malta fever, now known as *Brucella melitensis*, and the causal organisms of contagious abortion in cattle and in pigs, now known as *Brucella abortus*, and *Brucella suis*, respectively, and in 1920 the generic name *Brucella* was adopted.

Shortly afterwards, Bevan in India and Keefer in America recognized certain of the undulant fevers in man in these two countries as abortus fever transmitted from cattle and pigs, respectively.

Discussion.—In our present state of knowledge it seems justifiable to separate this group into the original Malta fever caused by *Br. melitensis*, and abortus fever caused by *Br. abortus* and *Br. abortus* var. *suis* (or *Br. suis*), as there are epidemiological and clinical differences between the two diseases.

MALTA FEVER

Definition.—Malta fever is a specific disease characterized by fever which may run a prolonged undulant course, effusion and pains in the

joints, and an enlarged spleen; it is caused by *Brucella melitensis*; and it is conveyed to man in the milk of goats, amongst which the infection is enzootic, and by other means.

EPIDEMIOLOGY

Geographical distribution.—Malta fever has a wide distribution and will be encountered in all the zones, except possibly the arctic, but the largest numbers of cases occur in the sub-tropics.

It is rife in the islands of the Mediterranean and in all the countries of the Mediterranean littoral, and it occurs in many other European countries. It occurs in the southern states of America, in Mexico, and in South America; in South Africa, in Iraq, Iran and northern India; in China, the Dutch East-Indies, and the Philippines; and in northern Australia.

Epidemic features.—The infection is an enzootic affecting goats and to a less extent other animals, and is transmitted sporadically to man by the ingestion of goat's milk or goat's milk products, and possibly by other means. Malta fever is therefore always likely to be present wherever goats supply the bulk of the milk to the population, and in Malta, until the means by which the infection is spread was discovered, the annual incidence amongst the British troops was often as high as 50 cases per 1,000. Thereafter it fell to a negligible figure, but from time to time for no obvious reason it has shown a tendency to rise again. The indigenous population also suffered, but they were usually affected in childhood when the disease is likely to be milder.

An incident in which 80 students in a hostel were infected, apparently by drinking-water, was recently reported from Michigan; there was in the building a bacteriological laboratory that handled large numbers of brucella cultures.

The incidence varies from year to year and is very definitely seasonal; in Malta it occurs in the hot dry months of the year, June to September (see figure 111). This seasonal incidence, which is also noted in other endemic areas, e.g. south-east France, where it is a little earlier in the year, is explained on the grounds that it corresponds with the kidding or lambing seasons, but there are other possible explanations (*vide supra*).

Persons of all ages are affected and the highest incidence is between the ages of six and thirty. Men are said to be most affected, but this may be due to the occupational factor.

The disease has an occupational distribution and is common amongst goat-herds and dairy and farm workers.

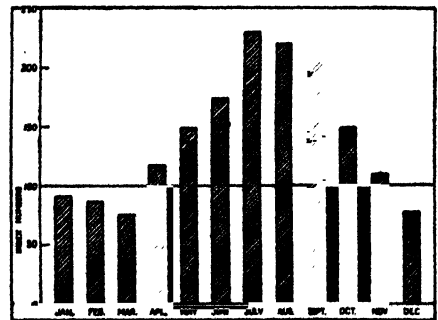


Figure 111: Seasonal distribution of Malta fever (Huddleson, 1934).

ÆTIOLOGY

The causal organism.—When first described by Bruce, the causal organism was named *Micrococcus melitensis*, but later when its relation to the other organisms causing undulant fever was recognized (*vide supra*), the genus *Brucella* was created and this organism was renamed *Brucella melitensis*.

Br. melitensis is a cocco-bacillus 0.3μ to 0.5μ in diameter, with oval or even bacillary forms which may be as much as 2.0μ in length. It is non-motile, non-sporing, and occurs singly, in pairs, or even in short chains. It is gram-negative.

Culture.—It grows on ordinary nutrient agar but very slowly; it will grow better but still slowly on liver-extract agar, or serum (5 per cent) agar, at 37°C ., and even at 20°C . It has a 'rough' variant that has different antigenic properties and was at one time thought to be a different organism (*Br. paramelitensis*).

Resistance.—It is killed at 60°C . but resists drying for two or three months. It will survive for many months in laboratory medium. Laboratory infections are relatively common.

Pathogenicity for laboratory animals.—*Br. melitensis* readily causes infection in monkeys, but not always in guinea-pigs, whereas *Br. suis* is very virulent in the latter; *Br. abortus* is very variable in its pathogenicity, but falls between the other two species in its pathogenicity in guinea-pigs.

Distribution in the body, secreta and excreta.—The organisms are present in the blood during the fever. They occur in large numbers in the spleen, from where they can be recovered during life by spleen puncture, or after death. They occur in the urine in about 10 per cent of cases, and the urinary infection may persist for some months. They have been isolated from human milk. They can also be demonstrated in the faeces by a special technique.

Portals of entry.—The usual means of infection is by the gastrointestinal tract, but the organisms can also enter with comparative ease through the conjunctival, nasal, or naso-pharyngeal mucous membranes, and also through the skin, but in the latter case, entry is probably effected through small abrasions. Laboratory infections are very common, and recently in the United States 57 laboratory infections were reported from 17 laboratories. The persistence of the infection in the British army and navy in Malta even after all consumption of goat's milk had been stopped, the higher incidence in the dry dusty season, the ability of the causal

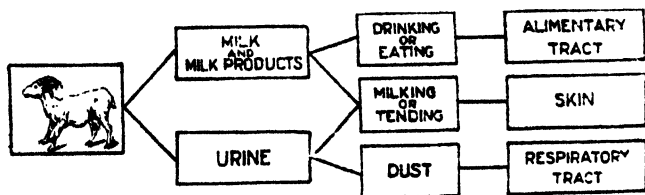


Figure 112 : Schema showing the origin, media and mode of transmission, and route of entry of the infecting organisms in Malta fever.

Differentiation of *Brucella* species.—There are two antigenic elements present in different proportions in the three allied organisms; the antigenic structures are shown diagrammatically in figure 113.

Thus, the organisms cannot be separated by straight agglutination, but *Br. melitensis* can be separated from the *abortus-suis* group by absorption of agglutinins. The brucellæ can also be differentiated by means of their growth in the presence of certain dyes; the following table, which is taken

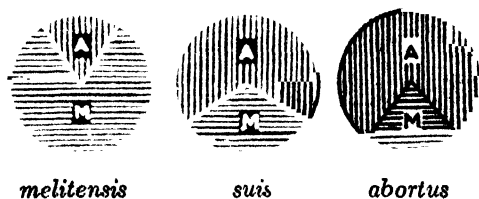


Figure 113 : Diagram indicating the proportions of the antigenic elements M and A, in the three recognized species of *Brucella*.

with minor modifications from Topley and Wilson (1936), summarizes the means of differentiation :—

Type	Usual habitat	Grown in absence of extra CO ₂	GROWTH IN PRESENCE OF				H ₂ S formation	Anti-genically
			Basic fuchsin 1 in 25,000	Thionin 1 in 50,000	Methyl violet 1 in 100,000	Pyranin 1 in 200,000		
<i>melitensis</i> ..	Goats, sheep	+	+	+	+	+	—	<i>melitensis</i>
<i>abortus</i> ..	Cows, horses, dogs.	—	+	—	+	+	+	<i>abortus</i>
American <i>suis</i>	Pigs	+	—	+	—	—	+	<i>abortus</i>
Danish <i>suis</i> ..	Pigs	+	—	+	—	—	—	<i>abortus</i>

Immunity.—One attack does not appear to confer complete immunity against a subsequent attack, but the second attack will be mild.

The fact that the organisms circulate in the blood for a number of days does not suggest the early formation of immune bodies; agglutinins usually appear, but they may be of low titre and are not constantly present.

No satisfactory immunity can be produced by inoculation of dead cultures.

PATHOLOGY

Morbid anatomy.—No clear-cut description of the pathological changes has been given; there are probably two reasons for this, namely, that there are few deaths and therefore few post-mortem examinations, and that such deaths as do occur are usually due to some complicating infection which clouds the true picture.

The spleen is nearly always enlarged; it is soft and hyperæmic. Occasionally, there are small hæmorrhages and infarcts.

Histologically, the sinuses are dilated, there is proliferation of the reticulo-endothelial cells, and a hyperplasia of the lymphoid tissue.

There is often slight enlargement of all the lymphatic glands, but especially those of the mesentery. In the intestines, there is sometimes slight congestion of a few Peyer's patches, but there is neither ulceration, nor even any other constant changes in the intestinal lymphoid tissue.

Degenerative changes have been described in other organs, but these are not constant and it is doubtful if they are specific.

Blood picture.—There is usually anæmia, and this tends to be progressive; red cell counts are sometimes below 3,000,000, but seldom if ever below 2,000,000 per c.mm. in an uncomplicated case. There is a slight tendency towards a leucopenia, but this is neither marked nor constant; however, the count in an uncomplicated case is never above 10,000 per c.mm. and sometimes as low as 4,000 per c.mm. The differential count is more characteristic; the lymphocyte count often amounts to 50 per cent of the total leucocytes, and there is a fairly constant large mononuclear increase, so that there is a relative, as well as an actual, granulopenia.

The urine does not show any special features beyond the usual febrile changes; it is high-coloured and scanty and may contain a trace of albumin. As noted above, brucellæ can be isolated from the urine in about 10 per cent of samples.

SYMPTOMATOLOGY

The incubation period is from 10 to 15 days, the extremes being from 5 to 17 days, as a general rule, but in exceptional cases it may extend to 40 days.

There are mild prodromal symptoms, malaise and headache, followed by a slow onset of fever, increasing lassitude and inability to concentrate, pains all over the body and particularly in the joints, pains in the eyes on lateral movement, anorexia, insomnia, and irritability. The fever increases step-ladder-wise, as in typhoid, and reaches 102° or 103°F. in five or six days. Headache may be intense, there is usually profuse sweating, and when the fever rises in the evening there may be a sensation of chilling, if not an actual rigor. The pains tend to move from joint to joint and the mandibular joint is very commonly affected; there is quite often a non-inflammatory hydrarthrosis of the painful joints. Mild abdominal symptoms may develop, congestion and discomfort usually with constipation, but occasionally with watery diarrhoea; the tongue is very furred. The pulse is soft, rapid, and irregular. Bronchial symptoms are common. The spleen may in time become enlarged; it is usually soft and tender. There is increasing toxæmia in severe cases, but in the average case the patient does not feel particularly ill, finds bed irksome, and is very irritable.

The fever reaches its highest point in about a week, it remains as a high remittent or continuous temperature for possibly another week, and then step-ladders down, reaching normal usually within three weeks; it



Figure 114 : Temperature chart of a case of Malta fever (orig.).

may remain normal for a day or two, and then it starts to rise again. The waves are not usually regular but on the average they maintain about a three-week periodicity. With the relapse of the fever, the symptoms tend to return but not usually in such a severe form, though sweating and fleeting joint pains are the rule.

Other symptoms are orchitis or mastitis, neuritis, *e.g.* facial and intercostal neuralgia, sciatica, and lumbago; and more rarely temporary paralyses. Sometimes there is blurring of the vision, and vertigo. In the long-continued cases, loss of weight and even emaciation will be an important symptom.

In severe cases there may be purpuric spots, oozing from the mucous membranes, and even profuse bleeding into the stomach, intestine, or bladder.

Complications.—Pulmonary complications are so constant that they can almost be considered a part of the syndrome; in fact the disease was at one time known as 'Mediterranean phthisis'. There is however no reason to believe that Malta fever does predispose the patient to pulmonary tuberculosis. The usual lung complication is bronchitis, but bronchopneumonia is not uncommon. Other complications are parotitis, purpurative orchitis, and arthritis; pregnant women usually abort.

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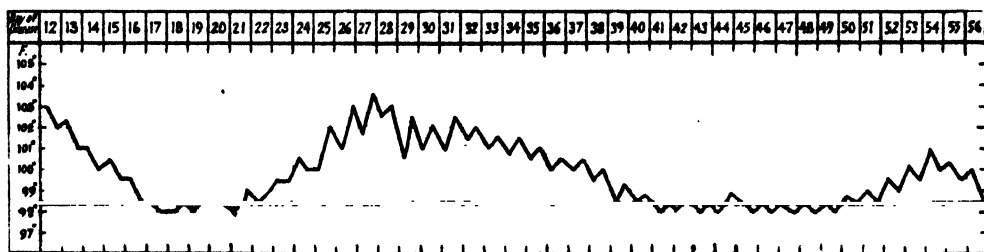


Figure 114 : Temperature chart of a case of Malta fever (orig.).

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Clinical types.—As in most other diseases, the individual's response to the infection will vary. The following clinical types can be recognized :—

(i) *The ambulant.*—In this type the patient is unaware of any illness, though in some cases, if pressed, he may admit to a little malaise. In any population subject to special risk, a serological investigation will bring to light some apparently healthy persons whose sera show a high agglutination for brucellæ.

(ii) *The mild.*—In this type there is only a single bout of fever lasting perhaps a fortnight, or a mild bout and one short relapse.

(iii) *The classical.*—The attack of moderate severity, as described above, with repeated relapses lasting several months.

(iv) *The chronic.*—The disease may start as an ordinary or mild attack, or in some cases there is no history of any acute febrile attack, and then a low irregular febrile state develops; there is little sign of the usual undulations in the temperature chart, but joint pains and sweating occur.

(v) *The toxic undulant or intermittent.*—In this type the patient develops a hectic type of temperature, he is much more toxæmic than in the ordinary case, and the temperature continues for weeks or months without the usual afebrile periods, though there are still some traces of the undulating character of the chart.

(vi) *The fulminant.*—There is early development of marked toxæmia, a high continuous or intermittent temperature running a typhus-like course, and sometimes death in as short a time as five days.

DIAGNOSIS

Discussion.—It is justifiable to make a provisional diagnosis on clinical grounds, and in certain circumstances it may be permissible to maintain it without confirmation from the laboratory, but, obviously, confirmation should be obtained whenever possible.

With proper laboratory facilities, it should be possible to isolate the causal organism in half to three-quarters of the cases seen early in the disease; in the remaining cases, and in those first coming under observation late, the specific tests will have to be relied upon. Of these, the agglutination test is the most reliable, the intra-dermal test should certainly be done in all suspected cases in which the agglutination test is negative, and the opsono-cytophagic test may be used as the third or as a confirmatory method.

A. Clinical.—The principal points are :—high fever with little prostration and with delay in the appearance of debilitating symptoms, profuse sweating and the maintenance of a moist skin during the height of the fever, and pains that pass from joint to joint. In retrospect, the undulant character of the temperature chart will be apparent.

B. Bacteriological.—A positive blood culture can often be obtained at almost any stage, but it is more certain in the early stages. Five cubic centimetres of blood should be taken into a flask containing 250 c.cm. of liver broth (pH 7.2); the air in the flask is displaced by CO₂, and a rubber cap put on; the growth is slow, and, though in some cases a positive culture may be obtained in about five days, a culture should not be discarded as negative for at least 12 days.

The urinary culture is said to be positive at some stage of the disease in 75 per cent of cases, but the general experience is that 10 per cent of specimens of urine will give a positive culture; the statements are not incompatible.

C. Specific antibody tests.—(i) **Agglutination.**—This is considered the most reliable of the specific tests, other than the isolation of the causal

organism; in most cases the agglutinins appear in the blood between the fifth and tenth days, and remain for a long but variable time, for many years in some cases and for one year in the majority. Agglutinins are not, however, constantly present even in the acute stages of the disease, and many cases have been reported in which they do not appear until the fourth or fifth week, so that a negative reaction does not exclude brucella infection.

A titre of 1 in 40 is usually considered to indicate infection, past or present, but the titre usually rises to over 1 in 1,000, so that a rising titre should be expected.

The agglutination test is not species-specific, and there is usually no significant difference between the titres obtained with *Br. melitensis* and *Br. abortus* emulsions, but, after the minor agglutinin (see figure 113) has been absorbed, agglutination will occur with the specific antigen with little reduction in titre.

(ii) *The intra-dermal test.*—The difficulty in this test is to prepare, or to obtain, a standardized antigen (or allergin). 'Brucellergin', as prepared by Huddleson (1934), is probably the best, but if neither this nor any other standardized preparation is obtainable, one can be made from a heat-killed fat-free bacillary emulsion. Reactions are apt to be sharp and there may even be constitutional symptoms, so that a 1-in-100 dilution of the standardized 'brucellergin' should be used first, and later, if a negative result is obtained, a 1-in-10 dilution.

A positive reaction varies from a 'weak reaction' in which there is an area of hyperæmia and slight œdema of half an inch in diameter to a 'strong reaction' in which there is an area of three inches or more of severe hyperæmia and œdema; this disappears in a few days leaving a small necrotic area in the centre, that may persist for months.

The injection is given intra-dermally, not more than 0.1 c.cm., and the result should be read after 24 and 48 hours, since a late reaction sometimes occurs.

A positive reaction may appear as early as the 7th day of the disease, and may be expected for many months after all symptoms have subsided. A higher percentage of positive reactions will occur with this than with the agglutination test, but occasionally 'false-positive' reactions are obtained.

(iii) *The opsono-cytophagic test.*—This test is a relatively simple one, but the interpretation of the results is somewhat complicated; it is the least valuable of the specific tests but it is used also as a means of estimating response to specific treatment.

Outline of technique and interpretation of results.—To 5 c.cm. of blood, 0.2 c.cm. of 20 per cent sodium citrate is added; a bacillary emulsion of 6,000 million organisms (or equivalent to a suspension of 300 parts per million of silica) in normal saline is made; one cubic centimetre of each of these two is mixed in a test-tube which is put into an incubator at 37°C. for one hour; the sedimented deposit is removed, and smears are made on clean slides; these are dried rapidly, the red cells hæmolyzed, and then the smear is fixed and stained. The slide is examined under the microscope and the number of polymorphonuclears that have taken up the brucellæ are counted.

The suggested interpretation is as follows :—

If less than 40 per cent have taken up brucellæ, the patient is susceptible.

If from 60 to 100 per cent have taken up brucellæ, the patient is immune.

A reading between these two indicates that immunity is developing and that the patient is therefore infected.

Differential diagnosis.—The disease may simulate any of the long-continued fevers of temperate or tropical climates.

The cosmopolitan diseases include—tuberculosis, especially of the lungs and intestinal tracts, the enteric fevers, rheumatic fever and rheumatism, *Bacillus coli* infections, and the Pel-Ebstein syndrome in Hodgkin's disease.

Amongst tropical diseases, kala-azar is the most likely to lead to confusion; there are many points of similarity: the long-continued undulating temperature—though in kala-azar the bouts of fever are usually of longer duration; the enlarged spleen—but this is usually more pronounced in kala-azar; the absence of prostration and the slow establishment of debility; and the granulopenia—which again is more marked in kala-azar. Untreated malignant tertian or relapsing benign tertian malaria, and also amœbic hepatitis with abscess formation may simulate Malta fever, but in both these diseases the therapeutic test should clear up matters, and in liver abscess there is *usually* a leucocytosis.

PREVENTION

The following are the three main lines along which attempts at prevention should be made:—

(i) The elimination of the source of infection, primarily in goats, sheep and cattle.

(ii) The prohibition of the use as food, or the sterilization, of the medium of infection.

(iii) The protection of susceptible and exposed persons, *e.g.* by education and if necessary regulations, and by inoculation.

(i) *The elimination of the source of infection.*—The destruction of the infected animals and the maintenance of disease-free herds is obviously out of the question, in view of the conditions that exist in most of the endemic areas. Protection of herds by vaccination would also be difficult to enforce, and up to the present this method, even when it has been put into operation, has not proved very successful, but this is a matter for further veterinary research.

It is probably very seldom that an infected person is a serious source of infection to others; nevertheless, viable bacteria may be passed in it urine and fæces, and the proper disposal of excreta is a preventive measure that should not be neglected.

(ii) *The prohibition of the use as food, or the sterilization, of the medium of infection.*—The prohibition of the consumption of milk or the products, or the enforcement of pasteurization will be successful only if the consumption of infected milk is the sole or main means by which infection is acquired. Even in Malta there is some doubt on this point though prohibition of the use of goat's milk and goat's milk products by the army and navy personnel appeared to be completely successful for many years. In other places, *e.g.* the south of France, where the disease occurs mainly amongst dairy workers, there are obviously other channels of infection.

Pasteurization will kill the brucellæ, and, if this procedure is strictly enforced, this means of spread of the disease will be effectively controlled.

(iii) *Protection of susceptible and exposed persons.*—Dairy and other workers should be warned to wash their hands before taking food, and to keep their hands free from abrasions.

The results of experimental inoculation with killed cultures of brucellæ have been contradictory, but on the whole very disappointing. More work will have to be done along these lines before this measure can be recommended as a routine.

TREATMENT

Discussion.—The state of the treatment of Malta fever is at present far from satisfactory. The introduction of the sulphonamide preparations raised hopes that a specific might be found for this infection, and many enthusiastic reports appeared in the medical press; these early reports were soon followed by cautionary, and eventually by frankly condemnatory

ones. As a new chemotherapeutic drug appears almost monthly, it is impossible to keep up to date, and it would be foolish to be dogmatic on this subject and to dismiss them all; further one hopes that some day a specific of this nature will be found. Meanwhile, it will be necessary to describe older, tested, though not uniformly successful, methods.

General, dietary, and symptomatic.—Even here it is not possible to be precise, since one has to deal with a wide range of clinical states. In the febrile stages, the patient should be kept in bed, and careful nursing should, if possible, be provided; the sweating will necessitate frequent changing of clothes; the bowels are usually confined and frequent enemata may be necessary; considerable trouble must be taken with mouth hygiene; the patient should be encouraged to take food in reasonable quantities and this will have to be presented in an attractive and palatable form; the joint pains will require local applications; and in the later stages massage to the wasted limbs will be helpful.

After a severe febrile bout, the patient should be kept in bed for four or five days after the temperature has fallen to normal, especially in a cold or temperate climate where chills are likely; later, when the disease enters on its more chronic stages, it will usually not be possible to maintain this routine, and it is questionable if it is necessary to limit activities, except during the febrile attacks. (Some writers recommend long-continued confinement to bed 'to obviate relapses'. In view of the very great variability in the clinical course of the disease, a controlled series of some hundreds of cases would have to be observed before the efficacy of this procedure could be proved. It does not sound reasonable to the writer and he has never advocated it.)

diet should be as liberal as possible, but naturally during the height of the febrile attacks it should be fluid; at other times it will have to be carefully selected for easy digestion, and it may have to be modified to meet such conditions as tympanites and diarrhoea.

Depressing drugs should as far as possible be avoided, especially anti-pyretics; for fever above 103°F. hydrotherapy should be employed. For Aches, aspirin, phenacetin and caffeine powders are permissible; now when a good night's rest should be ensured by giving phenobarbitone; (small doses of bromide may be given to soothe the patient's restlessness and irritability. Purgatives should be of the mild vegetable variety such as liquid paraffin, supplemented by enemata on alternate days if the bowels do not open. Joint pains should, as far as possible, be treated with physiotherapy (e.g. infra-red and local applications).

In acute toxæmic cases a pint of 5 per cent glucose may be given intravenously every day; this will combat dehydration, assist detoxication, and provide nourishment.

Vaccine therapy.—On the whole, vaccine therapy seems to have produced the best results, especially in chronic cases. The aim should be to produce little or no general reaction, and to grade the doses very carefully with this in view. Mixed stock vaccines may be used at first, but as soon as possible an autogenous vaccine should be prepared. The vaccine should be made from a 'smooth' recently-isolated human strain, and standardized so that 0.1 c.cm. given intra-dermally causes a sharp but not severe local reaction in an infected person. After an initial dose of 0.1 c.cm. given intra-dermally, the subsequent doses should be given subcutaneously every three or four days, the dose rising from 0.2 c.cm. up to 1.0 c.cm. or even higher, by increases of 0.1 c.cm., but the patient's reaction to each dose should determine the next.

Vaccines should not be given during the high febrile stages, nor when toxæmia is marked, and in these stages serum therapy is indicated.

Serum therapy.—This should be used only in the acute and toxæmic stages; several commercial anti-melitensis sera are available; doses of 50 to 100 c.cm. are given, preferably intravenously, in a pint of normal saline or 5 per cent glucose, and the dose repeated if necessary in 24 hours.

Non-specific protein therapy.—TAB vaccine or milk injections have been used. This treatment is indicated in the chronic low-febrile cases when joint pains are troublesome; good results have been claimed, particularly in relieving some of the tiresome symptoms.

Chemotherapy.—Dyes have been used for some time with varying results. Some success has been claimed for acriflavine; a maximum dose of 10 milligrammes per kilogramme body-weight, *i.e.* 0.7 gramme for the average adult, was given intravenously.

Trypaflavin has also been used; 10 c.cm. of a 2 per cent solution is given intravenously, once a week. A special precaution is that patients must be kept in a darkened room, as during this treatment they become very sensitive to light. Good results have been claimed with these dyes, but their administration is not entirely without risk.

Many of the new 'sulpha-' preparations have been tried, but so far, as stated above, without any uniform success. The writer has used sulphapyridine and sulphathiazole, without very convincing results. The chart of one case recently treated is shown (figure 115); it seems possible

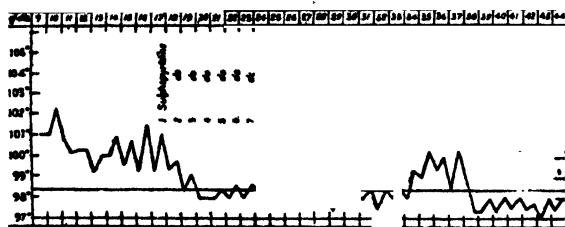


Figure 115: Temperature chart in Malta fever. Sulphapyridine appeared to control the fever, but a relapse occurred which again appeared to respond to sulphathiazole.

that the sulphathiazole controlled the fever, but our experience here is that a spontaneous cure often occurs after one or two bouts. Recent reports on sulphapyridine suggest that the history of the early reports on sulphonamide (*vide supra*) is being repeated. The writer has seen no reports on treatment with sulphadiazine.

Neither sulphanilyl-guanidine nor succinyl sulphathiazole, which are so useful in the dysenteries, is likely to be useful in this disease on account of their low absorption.

PROGNOSIS

The average duration of the illness in frank clinical cases is at least two months, but durations up to two years have been reported.

The death rate amongst such cases is from 2 to 5 per cent.

Published mortality percentages are open to the criticism that mild and ambulant cases are usually excluded. A comparison between the published death rates for Malta fever and the abortus fevers might indicate that the diseases were of equal severity, whereas Malta fever is undoubtedly the most serious, *Br. suis* the next, and *Br. abortus* the least serious of the three.

ABORTUS FEVER

Discussion.—As abortus fever is so closely related to Malta fever, only the points of distinction will be dealt with here.

Ætiology.—*Brucella abortus* and *Br. suis* (or *Br. abortus* var. *suis*) are morphologically identical with *Br. melitensis*: the cultural differences and certain other points of distinction are shown in the table on page 356.

Br. abortus and *Br. suis* cause enzoötic infections in cattle and pigs, respectively; cross infections, i.e. *Br. suis* in cattle and *Br. abortus* in pigs, are however possible and have been reported in nature, and other domestic animals, e.g. horses, are sometimes infected.

There is some suggestion on experimental grounds that *Br. suis*, unlike *Br. melitensis*, gains entry into the body more easily through the skin and mucous membranes than *via* the gastro-intestinal tract; this observation is supported by epidemiological evidence (*vide infra*).

EPIDEMIOLOGY

Geographical distribution.—Abortus fever has a much wider distribution than Malta fever, especially in temperate climates; it occurs in Great Britain, especially in Scotland, where Malta fever is unknown, and is very common in the United States, where the latter disease is relatively rare; there are few countries in the world, where the subject has been properly investigated, that can claim freedom from this infection.

Epidemic features.—Infection is transmitted from cattle and pigs to man in a number of ways, which are best shown diagrammatically; see figure 116 below.

Abortus fever has an even more definite occupational distribution than Malta fever, and is very prevalent amongst meat packers who handle pig carcasses, amongst stock-yard workers, butchers, and veterinarians, as well as amongst farm and dairy workers.

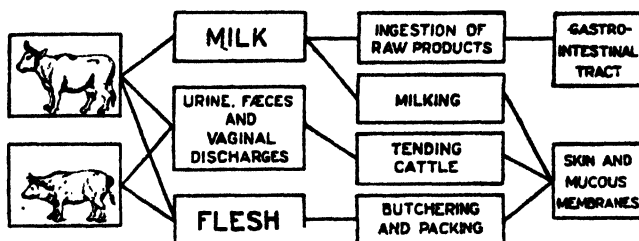


Figure 116

It is obvious that man is not very susceptible to *Br. abortus* infection, especially *via* the gastro-intestinal tract, as in both Scotland and America the infection rate in mixed samples of milk has been found to be over 30 per cent. In such circumstances one would expect the entire community to be infected; yet the reported cases number only some hundreds, in the former country at any rate. Further, this low morbidity rate cannot be altogether explained on the grounds of 'inapparent' infections, since there is no evidence of a high agglutination in the general population, though there is amongst certain communities.

SYMPTOMATOLOGY

On the whole, the disease tends to run a much more benign course than Malta fever; this applies particularly to *Br. abortus* infections. The vast majority of cases fall into clinical groups, (i) ambulant, (ii) mild, and (iv) chronic (*vide supra*); the more severe clinical types are rare but are encountered, and the death rate though low is not negligible.

The onset is slow and ill-defined. The commonest symptoms are malaise, headache, sweating, a marked tendency to lassitude and fatigue, vague body pains, rigors, constipation, and anorexia, more or less in that order of frequency, from 100 per cent down to about 60 per cent, in frank cases. The spleen is sometimes enlarged but less frequently than in Malta fever, and joint pains are less constant.

The fever is usually low and irregular throughout, but may be of long duration; in a relatively mild series of cases in Scotland, the average duration of the illness was ten weeks, but it is frequently longer, and durations up to two years are sometimes reported.

Br. suis infections are on the whole much more severe than *Br. abortus* infections; *Br. abortus* infections acquired in the laboratory seem to be much more severe than those acquired naturally. All *Br. suis* infections and laboratory infections with *Br. abortus* are nearly always acquired through the skin or mucous membranes, whereas natural *Br. abortus* infections are acquired *via* the gastro-intestinal tract. It seems possible therefore that the route of invasion has some effect on the severity of the infection.

The **prognosis** is distinctly better in *Br. abortus* infections than in Malta fever, and *Br. suis* comes between the two.

DIAGNOSIS

Under this heading, there is little to be added to what has been written above. However, a bacteriological confirmation of diagnosis is more difficult to obtain. On the other hand, the greater susceptibility of the guinea-pig to this infection can be taken advantage of, and guinea-pig inoculation should be added to the bacteriological methods.

Guinea-pig inoculation.—Two to five cubic centimetres of citrated blood should be inoculated intraperitoneally into a young guinea-pig, or the sediment from the centrifuged urine can be given subcutaneously into the flank or groin.

After four or five weeks the agglutination test is performed on the guinea-pig's blood, and, if the result is positive, the animal is killed and from the organs, particularly the spleen, smears and cultures are made.

Br. abortus infection in milk can usually be detected only by animal inoculation: 2 to 5 c.cm. of separated cream is injected into each groin.

REFERENCES

- | | | |
|------------------------------------|----|---|
| BANG, B. (1897) | .. | .. The Ætiology of Contagious Abortion. <i>Zeitschr. Tiermedizin</i> , 1 , 241. |
| BRUCE, D. (1887) | .. | .. Note on the Discovery of a Micro-organism in Malta Fever. <i>Practitioner</i> , 39 , 161. |
| EVANS, A. C. (1918) | .. | .. Further Studies on Bacterium Abortus and Related Bacteria. <i>J. Infect. Dis.</i> , 22 , 580. |
| HUDDLESON, I. F. (1934) | .. | .. <i>Brucella Infections in Animals and Man</i> . Oxford University Press, London. |
| HUGHES, M. L. (1897) | .. | .. <i>Mediterranean, Malta or Undulant Fever</i> . Macmillan and Co., Ltd., New York. |
| MARSTON, J. A. (1861) | .. | .. Report on Fever (Malta). <i>Army Med. Rep. London</i> , 3 , 486. |
| TOPLEY, W. W. C., and G. S. (1936) | .. | .. <i>Principles of Bacteriology and Immunity</i> . Edward Arnold and Co., London. |
| TRAUM, J. (1914) | .. | .. <i>Annual Report of the Chief, Bureau of Animal Industry</i> . U. S. Department of Agriculture, p. 30. |

MELIOIDOSIS

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Definition.—Meliodosis is a fatal disease of protean symptomatology, caused by a glanders-like bacillus, *Pfeifferella whitmori* (*pseudo-mallei*), which is transmitted to man sporadically from rats, amongst which it is epizootic, in certain eastern tropical countries.

Discussion.—The excuse for the inclusion in this book of a disease of which only about a hundred cases have been reported in the 30 years since it was first described, is that there are reasons to believe that it is much more widespread than our present knowledge appears to indicate.

Historical.—Whitmore and Krishnaswami (1912) described a disease that they had diagnosed post mortem in vagrants sent to the Rangoon mortuary. Attention was drawn to the disease again by an epizootic that occurred amongst the experimental animals at Kuala Lumpur. Its importance was finally established after the publication of a comprehensive report on the disease by Stanton and Fletcher (1932). These writers reported 83 cases of which 38 had been found in Rangoon and 14 had been diagnosed during 3,068 autopsies in Kuala Lumpur. This indicated a much higher percentage incidence than had previously been suspected, or has subsequently been observed elsewhere. Since then only sporadic cases have been reported, and, in fact, the disease has not really lived up to its early promise of establishing itself as a disease of public health importance.

ÆTIOLOGY

The causal organism, *Pfeifferella whitmori* (or *Bacillus pseudo-mallei*) is a motile gram-positive slender rod, 1 to 2 μ long by 0.4 to 0.5 μ broad, which shows a tendency to irregular or bipolar staining. The organisms grow well on ordinary solid laboratory media at 37°C. and on peptone agar producing a luxuriant growth in 24 hours, and form a pellicle in broth. They are killed easily by heat (at 56°C. within 10 minutes), but survive in water, fæces, and dried earth for a month or more.

In most laboratory animals, they produce a fatal septicæmia as well as a local abscess when injected. In the guinea-pig a small dose given intraperitoneally will cause a painful swelling of the testicles in two days (Straus's reaction); a large dose will kill the animal before this reaction has had time to occur.

Infection of animals will also occur after oral administration. The organisms are excreted in the fæces and urine of infected animals.

In man, it produces a septicæmia and/or a pyæmia, and can be recovered from most tissues of the body after death.

Transmission takes place mainly by the oral route, it is believed, by contamination of food by rat's fæces and/or urine.

EPIDEMIOLOGY

Geographical distribution.—The disease has been reported in Rangoon, Ceylon, Malaya, the Netherlands Indies and Indo-China.

Epidemic features.—It is a sporadic infection and little association between cases has been established; the exception being in Rangoon, where an outbreak occurred amongst a group of morphia addicts (injectors). It has been suggested (Stanton and Fletcher, *loc. cit.*) that this was a coincidence and did not indicate a parenteral route of infection in these subjects, though this deduction is the obvious one.

With few exceptions the patients have been vagrants or persons of the poorest classes, living under conditions of close association with rats.

PATHOLOGY

The essential pathological lesion is a nodular focus similar to miliary tuberculosis with a central area of necrosis that eventually forms an abscess. These occur in any organ or tissue except the central nervous system; however, in one case the organism was recovered from the cerebrospinal fluid. The main site of the lesions varies and in some cases they are confined entirely to the lungs; in others, only liver abscesses, very similar to amœbic abscesses, will be found.

SYMPTOMATOLOGY

Very few cases have been diagnosed ante mortem, and in these the symptomatology has shown wide variations. The earliest reported cases had cholera-like symptoms—a watery diarrhœa, vomiting and collapse, with death within two or three days; other cases have shown pneumonia-like symptoms and death has been postponed by several days, and in yet others a pyæmic condition has been reported, with subcutaneous abscesses or even a cutaneous eruption simulating smallpox. In this last group, the patients usually survive for two or three weeks, in some cases death has occurred after two months, and two patients have eventually recovered completely; these are the only non-fatal cases reported.

Other cases have simulated plague or typhoid.

Diagnosis.—Clinical diagnosis of a disease with such a varied symptomatology is out of the question. Bacteriological diagnosis presents no difficulties as the organism grows well in ordinary laboratory medium. Cultures can be obtained from the blood or from pyæmic abscesses. Where contaminating organisms are likely to be present, the material should be rubbed into a shaved area on the abdomen of a guinea-pig; this latter method will usually prove successful even with material taken from decomposed bodies.

A specific antibody that caused agglutination in a dilution of 1 in 3,000 was reported in the blood of one surviving patient. This method may prove of use for making a diagnosis in less acute cases.

Prevention and treatment.—In our present state of knowledge, no preventive measures other than the destruction of rats and the protection of food from contamination by these rodents can be advocated.

Treatment is entirely symptomatic. Obviously, the new chemotherapeutic agents should be given a trial.

Prognosis.—Only two patients have been known to survive.

REFERENCES

- STANTON, A. T., and FLETCHER, W. Melioidosis. *Studies, Inst. Med. Res., F. M. S.*, (1932). No. 21. John Bale, Sons and Danielsson, Ltd., London.
- WHITMORE, A., and KRISHNASWAMI, C. S. (1912). An Account of the Discovery of a Hitherto Undescribed Infective Disease occurring among the Population of Rangoon. *Indian Med. Gaz.*, **47**, 262.

THE INTESTINAL FLUXES

Introduction.—The treatment of fever and the intestinal fluxes forms at least 90 per cent of the daily routine of the practitioner in the tropics; in malarious districts, fever will probably claim the greater share of his attention, but even here the fluxes will come a close second; in other districts, they will be an easy first. The causes of diarrhœa are numerous and varied, and they may have their origin as far away from the intestinal tract as an examination paper. Diseases of nearly every organ in the body may lead to diarrhœa, as an important or an unimportant symptom. A number of cosmopolitan diseases, such as cancer, syphilis, and tuberculosis, as well as certain conditions of less well-defined ætiology, such as diverticulitis and regional ileitis (Crohn's disease), and mechanical irritation, may cause an ulcerative condition of the bowel which will produce the dysentery syndrome. No general classification will therefore be attempted, but here will be enumerated the more important forms of intestinal flux that have some special association with the tropics; most of these have a specific and recognized ætiology.

CLASSIFICATION AND DEFINITIONS

A. Cholera.—An acute specific diarrhœa caused by *Vibrio cholera*, in which the small intestine is mainly involved.

B. Dysentery.—A clinical condition in which frequent stools containing blood and mucus are passed, with tormina and tenesmus. Ætiologically, dysentery can be placed under a number of headings:—

I. Caused by bacteria.

(i) **Shiga dysentery.**—A very severe dysenteric condition, always acute in its early stages, caused by *Bacterium dysenteria* Shiga.

(ii) **Flexner-group dysentery.**—A dysenteric condition, sometimes severe, and usually acute in its early stages, caused by a group of organisms of the type *Bacterium dysenteria* Flexner.

(iii) **Sonne-type dysentery.**—A dysenteric condition, usually of a milder type, occurring in the tropics but common in non-tropical countries, caused by *Bacterium sonnei*, and other allied organisms.

(iv) **Diarrhœa and vomiting suggestive of food poisoning.** occasionally followed by dysenteric symptoms, associated with infections of the Salmonella group, *Salmonella paratyphosus-B*, *enteritidis*, and *typhimurium*.

II. Caused by animal parasites.

(a) **Protozoal dysentery.** (i) **Amœbic dysentery.**—Primarily a dysenteric condition, usually with an insidious but occasionally an acute onset, which is frequently followed by other acute and chronic conditions involving other parts of the body, caused by *Entamœba histolytica*.

(ii) **Flagellate dysentery.**—A diarrhœal and occasionally dysenteric condition, more common in children, caused by flagellate protozoa, *Giardia enterica* (or *lamblia*) which infests the duodenum and small intestine, and *Trichomonas hominis* and *Chilomastix mesnili* which infest the cæcum and large intestine.

(iii) **Ciliate dysentery.**—A rare but serious dysenteric condition caused by *Balantidium coli*, a ciliate common in pigs.

(iv) **Coccidiosis.**—A rare diarrhœal or dysenteric condition caused by *Isospora hominis*.

(v) **Malarial dysentery.**—A dysenteric condition associated with an intense *Plasmodium falciparum* infection.

Leishmanial dysentery is often included under this heading, but the evidence is against there being any such specific condition. In experimental animals, and to a less extent in man, the mucous membrane of the intestine is often heavily infiltrated by leishmaniæ, but histologically there is no tendency towards ulceration. The ulceration that occurs as a complication, often a terminal one, is due to some other infection, and/or to malnutrition.

(b) **Metazoal dysentery.** (i) **Bilharzial dysentery.**—A dysenteric condition, caused by the eggs of helminths of the genus *Schistosomum* (*Bilharzia*).

(ii) **Other helminthic dysenteries.**—Diarrhœal and dysenteric conditions caused by helminths of the genera *Æsophagostomum*, *Heterophyes*, *Fasciolopsis*, and *Strongyloides*.

C. Chronic ulcerative colitis.—A chronic non-specific ulcerative condition of the colon that is very frequently the sequel to one or other of the acute specific dysenteric conditions classified above: this is a condition that is well known in temperate countries but is far more common in the tropics.

D. Diarrhœal diseases that are probably dietetic in origin.

(i) **Sprue.**—A disease of disordered metabolism in which the passage of frequent frothy and fatty stools is a very prominent symptom, usually occurring in Europeans living in a tropical country, under abnormal dietetic conditions.

(ii) **Para-sprue.**—A diarrhœal disease due to multiple, often self-imposed, dietary deficiencies, associated with anæmia and disordered carbohydrate metabolism, and common amongst residents—indigenous and otherwise—of tropical countries, but not peculiar to them.

(iii) **Other nutritional diarrhœas.**—Diarrhœas that are important but not the main symptom of other nutritional diseases, e.g. pellagra (*q.v.*).

E. Diarrhœas of special local conditions.

(i) **Hill diarrhœa.**—A disease of mixed ætiology but possibly associated with the atmospheric conditions at high altitudes.

(ii) **'Gippy tummy' and allied conditions.**—A diarrhœal condition, probably mainly of bacterial origin, precipitated by local chilling, occurring in dry tropical and sub-tropical countries (e.g. Egypt) where there is a high diurnal range of temperature. (No further reference will be made to this condition, about which there has been much correspondence in the medical press recently: the general opinion is that it is usually caused by one of the recognized dysentery organisms and precipitated by sudden chilling.)

CHOLERA

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Definition.—Cholera is an acute specific often-fatal disease, characterized by very copious watery and colourless stools, vomiting, and symptoms attributable to fluid loss and toxic absorption, notably collapse, muscular cramps, and suppression of urine; it is caused by the cholera vibrio, and occurs endemically in certain localities in India and China and may spread as an epidemic throughout the world.

Historical.—The antiquity of cholera is doubted by many historians, and certainly there is little evidence that any of the early historical 'plagues' that fell upon countries and wiped out armies were cholera. In ancient Indian medical writings, Susruta described a condition that might well have been cholera, but the *χολερα* of Hippocratic writings was not this disease as the word literally means a flow of bile.

One of the earliest historical references to the disease is a reference to the destruction of Ahmed Shad's military force by cholera in 1438. Bontius described it in Batavia in the Dutch East Indies in 1629. Chinese writers have claimed that cholera reached China from India in about 1669, but there is a school of thought which claims that both Bontius and the early Chinese writers were describing dysentery.

The first and worst historical pandemic started in India in 1817 and spread in a number of directions :—(a) by land to China (1818); (b) to Ceylon (1819) and thence by sea to Mauritius and East Africa (1820), to the Philippines, China and Japan (1822); (c) by land to Iran (1822) and Arabia, and thence to Russia (Astrakhan, 1823); but this epidemic wave did not reach Europe. A second epidemic wave started in India in 1826, and followed a similar course, but on this occasion it spread further. It reached European Russia from two directions, *via* China, Manchuria and Mongolia, and *via* Astrakhan, and it reached Moscow in

September 1830; from there it spread to Leningrad (June 1831), Berlin (August), Hamburg (October) and thence across the North Sea to Sunderland in Great Britain, and it reached Edinburgh in June 1832. Later, it crossed to America.

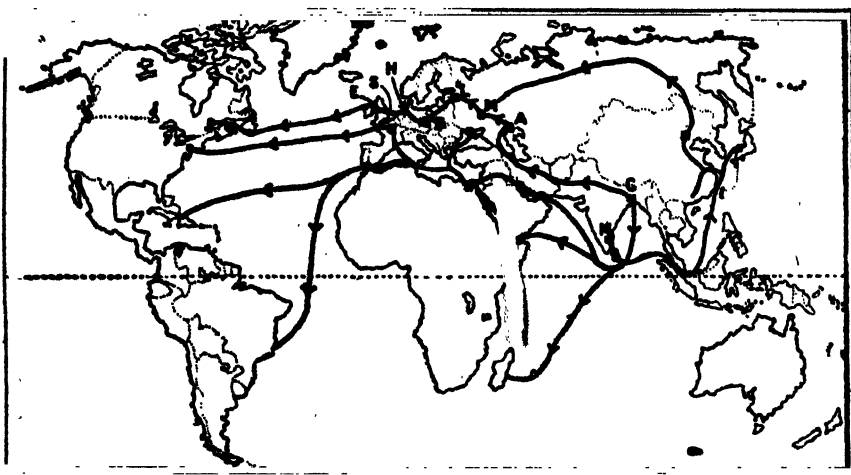


Figure 116 : Showing route taken by early cholera epidemics. Two epidemics starting from Calcutta (C) in 1826 and 1842, respectively, reached the following European towns at the dates indicated and then crossed to America :—

A Astrakhan	1830, 20th July	1847, June
M Moscow	" September	" 18th September
L Leningrad	1831, 16th June	1848, June
B Berlin	" 31st August	" June
H Hamburg	" October	" September
S Sunderland	" 24th October	" 4th October
E Edinburgh	1832, 22nd January	" 1st October

The pandemic of 1840 to 1849 also had its origin in India, and reached Europe overland; there were over a million deaths in Europe including 50,000 in Great Britain. The pandemic of 1863-66 travelled to Europe *via* Mecca and Egypt; this was used as an argument to oppose the Suez canal project which was at this time well under way. The next pandemic, that of 1884, was carried to Europe through the canal, and the 1892-94 pandemic taking this route reached Europe within five months. The last epidemic in America occurred in 1873.

Cholera has been described as the sanitarian's best friend. Its dramatic suddenness and obvious preventability disturb the complacency of the layman, and, just as the outbreak in England assisted Edwin Chadwick to get his Public Health Act of 1848 into the statute book, so in India the frequent epidemics of this disease have led to the strengthening of the sanitary services. In international sanitation, the successful control of cholera has done much to justify in the eyes of the public the strict and often very expensive and troublesome procedures which have been enforced, and which control the spread not only of cholera but of many other important diseases whose seriousness it is not so easy to demonstrate.

Throughout the greater part of the 19th century, from the time of the first pandemic in 1817 to 1883 when Koch discovered the vibrio, much controversy raged round the aetiology of cholera. The general view held was that cholera was caused by 'a poison of eastern origin', that certain climatic conditions were essential for its spread, and that it would only become established if the inhabitants of any particular locality were predisposed. General insanitary conditions were recognized as helping to generate the right atmosphere for cholera, but the theory of transmission by air was most favoured. Later, however, the Broad Street pump (1854) and the Newcastle epidemics fixed more and more attention on water as the source of the poison.

The idea of the micro-organismal origin of cholera had long been smouldering; Pouchet reported finding vibrios in the stools of cholera patients as early as 1849 (Scott, 1939). In 1883, Koch discovered the vibrio in the stools of cholera patients in Egypt, and later he came to India where at the Medical College in Calcutta he confirmed his theory by finding the same vibrio in the stools of every case of cholera that he examined. His theory was not accepted by everyone,

even in a scientific world ripe for the acceptance of any new bacteriological discovery. Some of the bacteriologists of the day seemed to think that Koch had displayed rather bad taste in introducing a curved organism where they had expected a straight one. His theory, however, soon received general credence, and the matter was left where it stood for some years. The application of the agglutination test and Pfeiffer's phenomenon at first seemed likely to clarify the problem, but it only gave scientific support to conclusions that were subsequently shown to be wrong, for, though it narrowed down the number of suspected vibrios, it brought under stronger suspicion a large group of innocuous ones—namely those now classified as group A vibrios other than sub-group I (*vide infra*), and at the beginning of the century the apparently harmless El Tor vibrio came to the fore, to remain a thorn in the flesh of bacteriologist and sanitarian for over thirty years. Confusion reigned and held up all real progress in the epidemiological study of the disease; the position was further complicated by much imperfectly controlled experimentation demonstrating mutations, and by the advent of the bacteriophage which threatened to lyse the whole science of bacteriology.

In this confused atmosphere, the Health Organization of the League of Nations constituted a cholera commission, and the Indian Research Fund Association decided to devote a considerable sum to cholera investigations. Bacteriological investigations in the Standards Laboratory at Oxford (Gardener and Venkatraman, 1935) and the National Institute of Medical Research at Hampstead, with the collaboration of field workers in India have led to a considerable clarification of the position as it stands to-day (*vide infra*).

ÆTIOLOGY

Classification of vibrios.—There are two main groups, group A—cholera and 'cholera-like' vibrios, and group B—other vibrios. The vibrios in these two groups are morphologically similar but biochemically and serologically very distinct, those of group B being far less active fermentatively. Group A vibrios are biochemically comparatively homogeneous, and they have a common H-antigen, but a number of O-antigens that divide this group into many sub-groups; the important one is O sub-group I, which includes the true non-hæmolytic cholera vibrio and the hæmolytic El Tor vibrio. Of the true cholera vibrios there are two sub-types, 'Inaba' and 'Ogawa'.

Thus, the true cholera vibrio is a non-hæmolytic vibrio that is agglutinated by pure O antisera prepared by means of the dried heat-stable O-antigens of the Inaba and Ogawa sub-types of O sub-group I. The position of the hæmolytic El Tor strains of sub-group I is still uncertain; in India, they have not been associated with any typical outbreak of cholera, and have been found in the absence of cholera, though in other countries, Celebes in particular, they have been the predominant, and the only suspected, organism isolated in epidemics that had all the clinical features of classical cholera.

The cholera vibrio: Morphology and cultural characteristics.—*Vibrio cholera* is a motile, comma-shaped organism, 1.5 to 4 μ long by 0.2 to 0.4 μ in thickness with a single polar flagellum, staining easily with weak carbol fuchsin, gram-negative, and growing easily on ordinary bacteriological media at 37°C. (*see plate II*).

On agar plates, the colonies are 'round, 1 to 2 mm. in diameter, low convex, translucent, greyish yellow with a smooth or finely granular glistening surface and entire edge, of amorphous or finely granular structure, of the consistency of butter, and easily emulsifiable'. On horse-blood agar plates, after 24 hours at 37°C. there is an abundant growth, and the colonies are surrounded by a 2 mm. zone of hæmolysis.

Biochemical reactions.—Heiberg suggested a classification of the vibrios on the basis of the production of acid in the three sugars, mannose, arabinose and saccharose: he observed that all vibrios of the serological sub-group I fall into his type I, namely, mannose +, arabinose — and saccharose +. However, many non-cholera vibrios also fall into this group.

The **cholera-red*** reaction is constantly positive with the true cholera vibrio if the peptone is of the right kind, but this also is not a specific test.

The modified **Voges-Proskauer†** test is with few exceptions negative with true non-hæmolytic cholera vibrios.

By carrying out these three tests, strong, though still presumptive, evidence is obtained regarding the identity of a true cholera vibrio; that is to say, with very few exceptions a true cholera vibrio will belong to Heiberg's type I, and will give a positive cholera-red and a negative Voges-Proskauer reaction, and if it does not conform with these criteria, it is probably not a true cholera vibrio.

Resistance.—The cholera vibrio has no resistant phase; it survives on clothes from one to three days in a moderately moist atmosphere, but is easily killed by drying. It dies in sea water within 24 hours. In pure water it dies rapidly, but in some 'potable' waters it will survive for a considerable time.

For the survival and multiplication of the cholera vibrio, salt and organic matter are necessary in the water; the higher the concentration of the former the lower need the latter be, and *vice versa*. The limits for multiplication are 1 per cent salt (sea salt) with 1 in 500,000 peptone, and 0.1 per cent salt with 1 in 500 peptone; for survival the range is distinctly wider; for example vibrios will survive for some weeks in 0.02 per cent salt and 1 in 5,000,000 peptone. The hydrogen-ion concentration limits are pH 6.0 and pH 9.4: the optimum is about pH 9.0.

Many natural waters in Bengal have an organic matter content equivalent to 1 in 5,000 to 1 in 300,000 peptone, and a salt content from 0.05 to 0.1 per cent.

It is killed at 55°C. in 15 minutes, in 0.5 per cent phenol in a few minutes, and in 1 in 500,000 potassium permanganate in 15 minutes.

Bacteriophage.—Up to the present, about 13 races of bacteriophage that lyse the cholera vibrio have been isolated; these are numbered from A to N. Two of these, A and N, are selective in their action, and act on the true cholera vibrio only.

Pathogenicity.—The cholera syndrome does not occur naturally in any animal species other than man, though a similar disease can be produced in very young guinea-pigs and rabbits; small laboratory animals are susceptible to the toxic action of the vibrios and to the products of their metabolism when morbid material is injected intraperitoneally or given by mouth in large quantities, but on subculture the toxicity is rapidly lost.

Laboratory infections have occurred and have been fatal, but they are comparatively rare and it is obvious that the organism loses much of its pathogenicity in culture.

Personal susceptibility also plays an important part; Macnamara reported an incident in which 19 persons ate a meal heavily contaminated by a cholera stool and only 5 developed classical cholera. An incident

* **Cholera-red reaction.** Ten cubic centimetres of peptone broth (peptone—1 per cent, sodium chloride—0.5 per cent, in distilled water, adjusted to pH 8.0) is inoculated with the vibrio culture to be identified, and incubated for 24 hours at 37°C. Four to eight drops of pure sulphuric acid are added. The development of a pink colour indicates a positive result. After the addition of four drops, the pink colour usually develops, but eight should be added before the reaction can be considered negative.

† **Barritt's modification of the Voges-Proskauer test.** Inoculate glucose-phosphate tubes rather heavily and incubate for three days. Add to 1 c.cm. of this culture 0.6 c.cm. of 5 per cent alcohol solution of β -naphthol and then 0.2 c.cm. of 40 per cent potassium hydroxide; shake well. A positive result is indicated by a pink colour that deepens and spreads throughout the mixture; read again in 4 hours.

Note.—It is essential that the β -naphthol should be of the correct brand and this must be tested with organisms of known identity. This precaution also applies to the peptone used for the cholera-red reaction.

happened in the writer's personal experience when cholera infection was introduced into the children's ward of a hospital, in so-called skimmed milk—probably milk diluted with dirty water—that he had ordered for a child with infantile cirrhosis of the liver. There were six children in the ward; two died of cholera, two had a mild diarrhoea, and two had no symptoms at all. From the stools of all six patients, cholera vibrios were isolated.

Toxins.—This is always a controversial point. The general opinion is that there is no true soluble exotoxin secreted, but that there is an endotoxin liberated by the disintegration of the vibrios on their death in the intestinal canal or when lysed by the cells of the body. It has not been possible to isolate this endotoxin in sufficient quantities to produce a satisfactory anti-serum. It is possible that, although the vibrio does not produce an exotoxin *in vitro*, it may do so *in vivo*.

Distribution in the body.—The vibrios are confined almost entirely to the gastro-intestinal canal, mainly to the lumen, and they are usually found in large numbers throughout its whole length. They do not penetrate further than the submucosa. The gall-bladder and biliary passages are sometimes infected, and the vibrios have been isolated from pneumonic patches in the lungs.

Mode of escape from the body.—Vibrios escape from the body in the stools and in the vomitus, but recent investigations have shown that they cannot be isolated from the urine, if measures are taken to avoid faecal contamination of the urine (Chatterjee and Malik, 1938). The patient does not usually pass true cholera vibrios in the stools for more than five days from the time of first infection; this is also true in the sub-clinical (or contact) case of cholera infection. In a few instances, 'carriers' have been detected who passed cholera vibrios up to two weeks, but it is very doubtful if there is a true carrier state in cholera as there is in typhoid (Taylor, 1941); in this connection, reports previous to 1935 must be discounted, on account of the doubt that exists regarding the true identity of the organisms passed. The human source of cholera infection is thus cases and contacts (sub-clinical cases).

Route of invasion.—Infection always occurs by the oral route. There is no reason to believe that the vibrio is capable of establishing itself after entry by any other route. This means that there is no danger from attending cholera patients if food is not taken until the attendant has washed his or her hands and changed his or her clothes.

Gastric acidity is apparently an important factor in determining the establishment of infection when the vibrio is ingested (Napier and Gupta, 1942); vibrios are killed immediately in undiluted gastric juice of normal acidity.

Media of infection.—The commonest medium of infection is water. Other fluids also, particularly milk, will carry the infection. Uncooked foods and any food allowed to remain uncovered are common media of infection, especially during an epidemic; *e.g.* fruit and vegetables which may have been sprinkled with water taken from any wayside source, to keep them fresh; food exposed for sale in the open bazar and by itinerant sweet-meat vendors; and food, cooked or otherwise, remaining over from one meal and left exposed before being eaten, without further cooking, at the next.

Active agents of infection.—The domestic fly is by far the most, and probably the only, important active agent, though the cockroach and the rat should not be entirely excluded as possible mechanical conveyors of morbid material.

Immunity.—There is evidence that, in man, some—though possibly not complete—natural immunity exists. It has been claimed that new-

comers to an endemic area are more susceptible than the indigenous inhabitants, but in this disease there is much less evidence of acquired herd immunity in the endemic areas than there is in the case of many other endemic diseases, for periodic exacerbations frequently occur with very high incidence and death rates.

One attack does not give protection against a subsequent attack. Though a second attack within a few years is uncommon, the author knows of two instances in which patients had three attacks of cholera within 16 and 10 years, respectively; in the former case, two of the attacks were bacteriologically proven, and in the latter, one attack was bacteriologically proven, but all three were typical severe attacks and the second was the most severe.

Active immunity can be induced by inoculation, but it is very short-lived and lasts only for six months at the outside.

Active immunity can be induced in animals by the injection of killed cultures of the vibrio; with this active immunity a specific agglutinin appears in the blood. Rabbits are the most suitable animals for the preparation of the specific agglutinating sera that are used in the serological identification of vibrios.

On account of the lability of the agglutinin, standardization is maintained by the preservation of standard O-antigens in the dried state. These are prepared at the Standards Laboratory, Oxford, and are issued to workers in various countries. From these O-antigens, agglutinating sera are prepared by a standard method.

Predisposing factors.—Individual susceptibility is an important factor, though probably few people enjoy complete immunity. What is the determining factor in infection is not of course certain, but it has been shown that gastric acidity is very important. When this is high, the vibrios are killed almost immediately, whereas in achlorhydric gastric juice they survive for a considerable time. It is probably for this reason that water is such a common medium of infection, as it dilutes the gastric juice and passes rapidly through the pylorus. Starvation, exhaustion, and debility from other infections in a population are important factors in determining the severity of an epidemic, but healthy and strong individuals will also be attacked. Gastro-intestinal disturbances, alcoholism, and excessive purgation are usually considered to predispose to infection.

EPIDEMIOLOGY

Endemic centres.—The most important epidemic centre of cholera in the world is undoubtedly in Bengal; the origin of most epidemics in India, some of which have become pandemics, can be traced to Bengal, but there is evidence that there are, now at least, several subsidiary centres from which cholera is capable of originating. In India, there is apparently another endemic centre in central and south Madras. The frequent outbreaks that occur in China, only a few of which could be traced to India, make it certain that there are endemic areas in that country, but these appear to be confined to the Yangtse valley. Recent investigations have suggested that there are endemic areas in Burma and the Philippines, but Indo-China and Thailand, which were at one time under suspicion, have recently been exonerated.

In Bengal, the endemic area is not as extensive as was previously supposed, and to date, only the districts of Khulna, 24-Parganas, Midnapore, Howrah, Hooghly, Bankura and Birbhum are definitely known to be endemic. These districts are all located on the banks of the Hooghly river. The criteria of endemicity that the sanitarians have adopted are :—that in a period of 32 years cholera should not have been absent for more

than thirty months, or, during the whole of this period, for five consecutive months. This statistical test has not yet been applied to all the districts in Bengal and Madras where endemicity is suspected. Figure 117 gives only a rough indication of the endemic areas, and in time will have to be revised.

It should be appreciated that, in any particular year, the incidence of cholera in an epidemic area may far exceed that in the endemic area from which the infection originated.

The origin and maintenance of infection.—

Cholera is an eminently preventable disease, because, as far as is known, the origin of infection is invariably a human being. Although the alliterative

trinity, the case, the contact, and the carrier, is always mentioned in the tenets of belief of the sanitarian, they are not in fact three sources but one source, for the contact is a sub-clinical case of cholera and the carrier is only a prolonged one. There is no known animal source of infection and the true vibrio has not been isolated from any natural source in the absence of cholera for more than a few weeks.

The maintenance of the infection in the endemic areas has always interested bacteriologists and epidemiologists; survival and multiplication in village water supplies for many weeks is possible (*vide supra*), but the present opinion is that there is no other residual source of infection in the endemic areas except cases, and that infection is maintained mainly by case-to-case passage of virulent non-hæmolytic O sub-group-I vibrios. In the vast majority of the villages in the endemic areas, the sanitation is of the most primitive nature; there are no latrines and no protected water supply. The people use the open fields and frequently the banks of 'tanks' (reservoirs) for defæcating. Open tanks are their only water supply, and they will bathe in the tanks, wash out their mouths, and even drink the water at the same time.

Epidemic extension.—The source always being human, the spread of infection must necessarily be along lines of human communication, and the speed with which the disease has spread in the past has always been controlled by this fact. The early pandemics spreading overland to Europe took four to five years in their journeys from the banks of the Hooghly to those of the Clyde, the St. Lawrence, and eventually the Mississippi, whereas in the later pandemics when the infected persons passed through the Suez canal, the infection only took as many months to reach northern European ports (*vide supra*). To-day, were other conditions favourable to cholera spread, we could expect pandemics to spread through the world within a week or so.

In India.—With the very great increase in facilities for travel, the chances of spread of cholera from the endemic areas to other parts of India are considerable, but it has been found that normal railway travel on business or pleasure does not tend to spread the disease to any great extent on account of the control that can be exercised over passengers, and

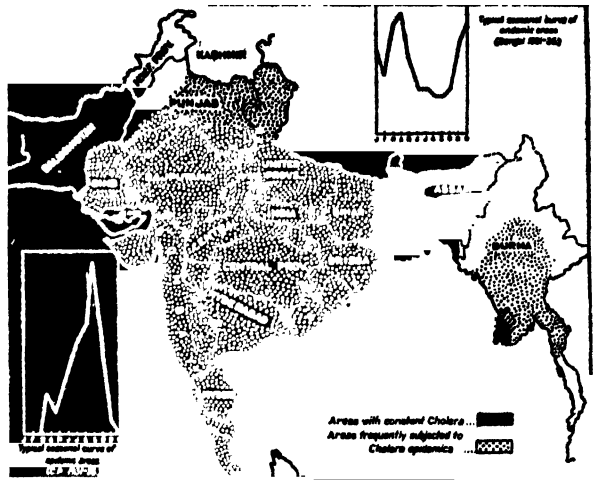


Figure 117

that, though the sanitary arrangements are far from perfect, especially at the small stations, there are latrines and a safe water supply. Such travellers of course come from all grades of society, but even the poorest are seldom destitute, and the fact that they are travelling usually indicates that they can afford the ordinary necessities of life.

By far the greater danger comes from pilgrims going to holy places, *e.g.* Benares and Puri, often many hundreds of miles away from their homes, and from the visitors to the religious *melas* (fairs) that are held from time to time in certain places. The people who attend these are often extremely poor, and such money and food as they have when they leave their homes are soon finished, so that they arrive in an ill-nourished and exhausted state. Further, it is difficult to make satisfactory sanitary arrangements for the literal millions that attend some of these *melas*, *e.g.* the Kumbh mela at Hardwar, at which the attendance has been estimated at over a million on certain days. Those pilgrims who come from the endemic areas, and others who travel through such areas, take the infection with them and spread it widely amongst other pilgrims, who in due course take back the infection with them, and, returning to their homes all over India, leave trails of cholera throughout the country as they go. As recently as 1930, an epidemic which caused 140,000 deaths in Bihar and the United and Central Provinces followed the Kumbh mela at Allahabad.

The extension of epidemics **outside India** has in recent years been almost entirely by the sea routes, and with improved port sanitation and sound quarantine regulation, this extension has been largely controlled. Here again, pilgrim traffic has been the main difficulty, and the Mecca pilgrimages are, probably rightly, thought to have been the most potent factor in carrying the infection to Europe; here devout Muslims from India live in close contact with those from Egypt and Turkey, and the danger of the infection being carried back to the countries would be considerable unless special precautions were taken.

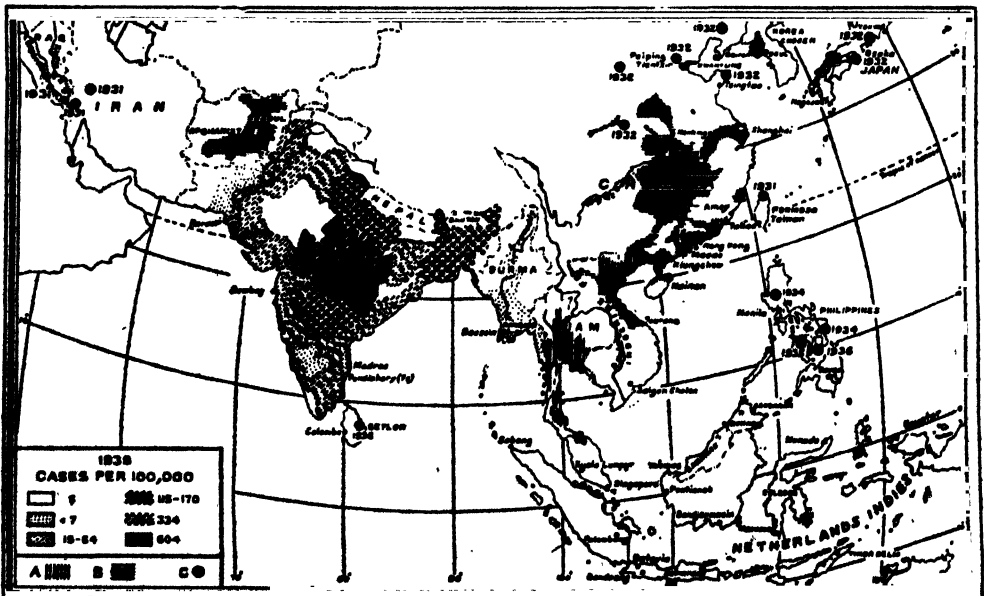


Figure 118 : Geographical distribution of Cholera in Asia, 1930-1938 (*League of Nations' Weekly Epidemiological Record*).

A. Disease reported in 1937.

B. Disease reported in 1938.

C. The dates shown on the map for the various territories correspond to those of the latest occurrence of the disease.

Climate and cholera.—The importance of climate in determining cholera endemicity is obvious from the similarity of the climates in all the endemic area, but it is also obvious that climate is not the only factor. The endemic areas are all areas of high humidity and relatively high temperature throughout the whole year. Humidity appears to be the more important factor, for it determines the epidemic spread of the disease as well; temperature appears to be less important in this respect, for cholera spreads rapidly in cold countries. Attempts to delimit the endemic areas on climatic criteria alone have not been entirely successful. Rogers' criterion of an absolute humidity of 0.400 inches of vapour pressure throughout the year can be accepted only in that this constant high humidity is a common feature of all the true endemic areas, but it is not correct to suggest that all areas with this degree of humidity are endemic areas, even in India.

Seasonal incidence.—The factors that determine this are different in the endemic and epidemic areas.

In the **endemic areas**, temperature and absolute humidity are the main determining factors; in Bengal, for example, in January, when the absolute humidity is low and the temperature relatively so, cholera, though present, is at its lowest incidence. As the temperature of the air rises so does its water-carrying capacity; cholera incidence rises steadily until May or June when the monsoon sets in, the humidity rises but the temperature falls, and obviously some other factor also comes into operation, for cholera incidence declines; this other factor is probably the mechanical flushing of contaminated water supplies and the alteration in their chemical and physical character. Cholera incidence shows a rise in October as the monsoon subsides, and it falls again at the end of the year when temperature and both relative and absolute humidity fall.

In the **epidemic areas**, on the other hand, the cholera incidence curve follows the absolute humidity curve throughout the year, reaching its peak in the monsoon months, July to October (figure 117).

Variations from year to year: forecasts.—In both the endemic and epidemic areas there are considerable variations in the incidence from year to year, more especially in the latter; the factors bringing about these variations are not solely climatic, but where and when other factors, *e.g.* the social and economic, are fairly constant, the cholera incidence follows closely certain climatic occurrences, and it is possible to foretell with a considerable degree of accuracy the probability of an epidemic occurring, some time ahead of the actual event. For example, when an early rise in humidity in the epidemic areas occurs and precedes the monsoon decline in the cholera curve in the neighbouring endemic area, an epidemic is likely to follow. Also the failure of the monsoon in one year is likely to be followed by an epidemic in the next year, and after two such successive failures, an epidemic is even more certain.

The importance to the local sanitary staff of knowing what the chances are of cholera occurring in the epidemic areas, or of the incidence being abnormally high in the endemic areas, is obvious, and has led to a very serious study being made of the cyclical incidence of cholera and of the climatic and other factors that influence it. A number of methods of **forecasting** have been devised, but on the whole Rogers' (1933) method has been the most successful; it also has the advantage of not requiring such a high degree of knowledge of statistical methods. Another method of forecasting, that depended on the observation of the cholera incidence in the last few weeks of the year as indicating the probable incidence in the following year, has been successful in a number of districts in the endemic and sub-endemic areas in Bengal. The subject however is too technical to be

undertaken by the average practitioner, as well as being outside his sphere (Russell, 1925; Lal, Raja and Swaroop, 1941).

Race, sex, and age distribution.—There appears to be little difference in the susceptibilities of the different racial elements in the population, and, even in the highly endemic areas, the indigenous inhabitants are very susceptible. Men are said to be more frequently affected than women, but it seems possible that there has been a selective tendency in the data on which the statement is based. There are also relatively fewer children than adults amongst hospital patients admitted with cholera, but children are susceptible, and in them the disease will usually run a severe course; an infant aged two months with cholera was recently admitted to a Calcutta hospital.

PATHOLOGY

Morbid anatomy.—The body is dehydrated, though usually well-nourished as the illness is a short one. There is marked early post-mortem rigidity; in some cases the stiffening of the limbs is almost ante-mortem. The muscles are dehydrated, dark red, and firm, and show curious post-mortem contractions which in some cases are so marked that they have been known to cause a body to fall off the post-mortem table. It has even been suggested that some of the instances in which bodies have been reported as having turned over in their coffins, and which have been quoted as examples of live burial, are really cases in which such muscular contractions have been extreme.

In the abdominal cavity the omentum will be found as a sticky curled-up mass; the serosa, especially of the stomach, duodenum and small intestine, are pink; the lymph follicles are slightly enlarged; and the contents of the bowel are the typical rice-watery alkaline fluid in which there are flakes of mucus and sometimes streaks of blood. The mucous membrane of the stomach, the small intestine and often the large intestine are congested, and there may be petechial hæmorrhages.

The liver is congested and full of dark viscid blood; there may be some toxic degenerative changes in the parenchyma cells, especially if death took place in the later stages. The gall-bladder is full, and the viscid bile will not pass along the ducts even when the gall-bladder is squeezed. The **spleen** is usually small and contracted. The **pericardium** often shows petechial hæmorrhages; the right heart and the large veins are full of dark tarry blood. The **lungs** are usually shrunken and anæmic, but, if death occurs in the later stages, especially when the intravenous saline therapy has failed, they may be œdematous.

The **kidneys** may show intense congestion, with effusion and occasionally hæmorrhages into Bowman's capsule and between the tubules, the latter being filled with a colloidal hyaline material. Focal necrosis in the glomeruli has been reported.

On the other hand, in many cases, the kidneys show no apparent pathological changes, and there is a strong suggestion that the kidney failure is mainly extra-renal in origin (*vide infra*).

The kidney changes are more in the nature of a nephrosis than a nephritis, and complete and rapid recovery of kidney function may be expected in non-fatal cases; on the other hand, previous damage to the kidneys adds very considerably to the gravity of the prognosis, so that some of the changes in the kidneys that are reported may be due to causes other than the infection that caused the death of the patient.

The above is the characteristic picture, but in some cases there are no apparent changes in any of the organs, and in others in one or two organs only; the most constant changes are those due to dehydration.

The cholera vibrios are confined almost entirely to the gut lumen (*vide supra*).

The blood.—On account of the dehydration, there is often a polycythæmia, the red cell count not infrequently rising to 7,000,000 per c.mm. or more. There is a disproportionate leucocytosis, often up to 20,000 per c.mm., with a relative large mononuclear increase. The red cell volume percentage which is normally 45 to 48 may rise to 65.

The sedimentation rate is increased in the majority of cases, but not markedly; it would appear that there are two opposing influences, because it is mainly in the serious cases in which the specific gravity of the blood is high that the sedimentation rate is within normal limits (deMonte and Gupta, 1941).

With the suppression of urine, the non-protein nitrogen and urea are raised considerably, but it returns to normal comparatively rapidly, usually within a week after the urinary flow has started again.

As pointed out by Rogers (1911) in his early investigations that led to the adoption of the hypertonic and alkaline saline treatment, there is a great reduction in the alkaline and the chloride reserve, with resultant acidosis and retention of nitrogenous waste products that will further increase the renal failure. Banerjee (1941) has shown that in an average case, 10 grammes of sodium chloride may be lost in the vomitus and 35 grammes in the stools in 24 hours. Rogers also claims that the chloride combines with and neutralizes the 'cholera toxins'.

Dehydration.—In the severe case of cholera, the symptoms are mainly due to dehydration and loss of chlorides and alkalis (*vide supra*). The similarity between a patient with cholera and one in shock, *e.g.* from a burn, is very great, but not complete, for, in the latter, there is loss of all the plasma elements and not just fluid and electrolytes as in the former (*see* figure 119).

The best measure of dehydration is the specific gravity of the blood; the 'normal' specific gravity of the blood is given by Scudder (1940) as 1.0566 in men and 1.0533 in women. In Indians, we usually consider 1.054 as normal; in cholera it may rise to 1.064 but very seldom higher.

Renal failure.—It is easy to understand how hæmo-concentration, circulatory failure through loss of blood volume, and some degree of toxic vasomotor paresis with resultant hæmostasis, will lead to failure of the renal circulation, and therefore of renal secretion, until the blood pressure improves and/or the specific gravity of the blood is lowered by saline infusions. The urinary flow will practically never start while the specific gravity of the blood is above 1.060, and seldom while this remains above the normal level, or while the systolic blood pressure is below 100. Further, in cases where the renal inertia is of long standing, this is not readily overcome, and it seems very possible that in some cases the temporary ischæmia during the period of circulatory failure will have caused some irreversible changes in the kidney that may not be apparent histologically.

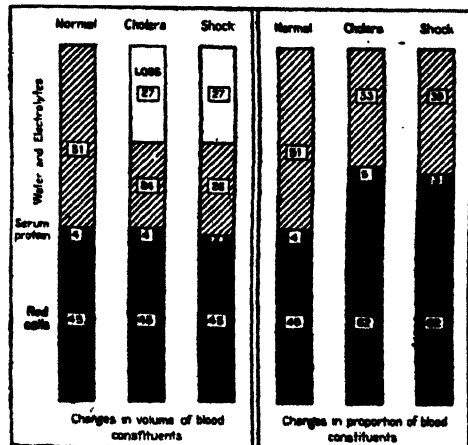


Figure 119.

The urine.—The urine, prior to suppression, will be highly coloured, have a specific gravity above normal, and show a distinct cloud of albumin.

After suppression, the first urine passed will contain a high percentage of albumin, and hyaline, granular and epithelial casts. The specific gravity will be within the normal range, between 1.010 and 1.020. The chloride content may be as low as 0.1. This first 24-hours' urine will be small in quantity, and its urea content very low, as the kidney is not yet able to concentrate urea. During the next few days, with the rapidly increasing efficiency of kidney function, more urine will be passed and the urea content may rise above normal. Subsequently, with more fluid intake, the urinary output will increase further and the urea percentage again drop.

SYMPTOMATOLOGY

As has been shown above, there are many instances of cholera in which there are no clinical symptoms; such instances (contact carriers) are important from an epidemiological point of view (*vide supra*). From a clinical point of view, cholera infection may produce any one of three types of cholera :—

(a) *Mild*—choleraic diarrhœa.

(b) *Typical severe cholera*, with purging and vomiting.

(c) *Cholera sicca*, a comparatively rare, very severe form of cholera in which the toxæmia is extreme, causing paralysis of the bowels, so that the patient dies within a few hours, after some vomiting but no diarrhœa; the bowels are found distended with rice-watery fluid, laden with vibrios.

It will be appreciated that there is no sharp line of distinction between these three types, and it will be sufficient to describe the typical attack.

The incubation period is short; it is probably never longer than five days, usually less than three, and sometimes the first symptoms appear within 24 hours.

The onset may be with a moderate diarrhœa which develops in severity, but it is much more frequently sudden with violent purging and vomiting. After the lower bowel has been emptied of fæcal matter at the first few purgings, the stool takes on the typical rice-water appearance, a non-offensive whitish fluid with flakes of mucus and occasionally streaks of blood. The diarrhœa is profuse and painless—described alliterately as pints of pale fluid painlessly pouring away. The diarrhœa is shortly followed by profuse watery vomiting. This constitutes the **first stage**, or **stage of copious evacuations**, and its duration will vary inversely with the severity of the symptoms.

The patient then passes into the **second stage**, the **stage of collapse**. The purging and vomiting continue, the former becoming a continuous process and the latter being uncontrolled and often precipitate. The classical cholera facies are assumed—the eyes sunken and cheeks hollow, the skin cold and clammy to the touch and cyanotic, the fingers shrivelled (washer-woman's fingers), the voice husky, and the expression anxious; the patient complains of extreme thirst, and becomes very restless; the blood pressure falls and the pulse cannot be felt at the wrist; the surface temperature may be as low as 95°F.; the rectal temperature at the same time may however be normal, or even slightly raised; there are severe cramps in the muscles, particularly of the legs; and the urine will be suppressed. Death may occur in this collapse stage from circulatory failure, or from asthenia; the mind usually remains clear until the end.

If the duration of this algid stage has only been a few hours, the **third stage**, or the so-called **stage of reaction**, will be the stage of recovery; the purging and vomiting having stopped, the blood pressure and the temperature will rise to normal, urine will start to flow again, and the patient will

slowly recover. But if the algid stage continues for long, the 'stage of reaction' may be as serious as the earlier stages. The usual explanation of this reaction is that the recovery of the circulation means more blood flowing through the intestinal blood vessels, and more absorption of toxins. However, if the kidney failure has been long continued and/or there has been organic damage to the kidney parenchyma, caused by the ischæmia, or by the problematical toxin, the urine may not start to flow again, and a cholera-typhoid state may supervene. In rare cases the temperature rises very high, and this necessitates hydrotherapy. Cholera has been described as a disguised febrile disease, the fever being suppressed in the collapse stage; the writer questions this interpretation, and doubts whether the rise of temperature that occurs in a few cases is really part of the cholera syndrome. He has seldom seen any febrile reaction in an uncomplicated case that could not be accounted for by the infusion of pyrogen-containing saline. The charts of ten consecutive cases are shown in figure 120; in one case the rectal temperature was high on admission, but in no case was there any reaction rise.

Death may occur in this stage from toxæmia, azotæmia, hyperpyrexia, or from one of the various complications that may appear (*vide infra*). Anuria will usually result in death within four or five days, but there have been instances in which the patient has passed into a semi-comatose state and died on the 9th day of the anuria; recovery has been reported after anuria for four days.

The recovery may be temporarily accompanied by the passage of a little concentrated urine with a high percentage of albumin and many hyaline and granular casts; when the blood pressure falls again, the patient will once more become anuric. When, however, the patient passes as much as two pints of clear urine in 24 hours, the danger of relapse has usually passed.

Convalescence is usually comparatively rapid, but great care should be exercised, as sudden heart failure as the result of slight exertion is not uncommon.

Complications.—Enteritis and diarrhœa, pneumonia, parotitis, sloughing of the cornea, cholecystitis, and abortion in pregnant women are amongst the common complications; pneumonia is common in cold countries but comparatively rare in the tropics. Gangrene of the extremities, penis, and scrotum are mentioned in the textbooks as being the result of long-continued collapse, but are seldom seen in these days.

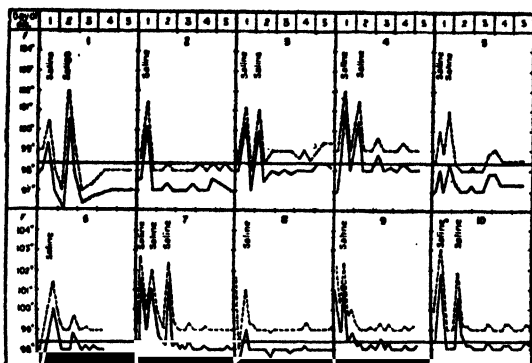


Figure 120: Temperature charts of ten consecutive cases of cholera (broken line = rectal temperature). Only in cases 8 and 9 was there any fever at the time of admission, and none had any fever up to the time of discharge (usually 7th to 10th day) except when saline was given; this was not made with pyrogen-free water.

DIAGNOSIS

In the large majority of cases, and especially during an epidemic, it will be possible to make a clinical diagnosis with a considerable degree of certainty. In fact, during an epidemic, all suspected cases should be treated as cholera, and all contacts as potential cases of cholera and as probable

cases of vibrio infection. The diagnosis of the isolated case is more important from a public health point of view than from the patient's, for, when there is severe purging and vomiting with consequent dehydration, the intravenous saline treatment is indicated whatever the ætiology.

Even without full laboratory facilities, a provisional bacteriological diagnosis can be made by examining wet and dry films under the microscope; the latter is made by taking a shred of mucus from the stool, making a smear on a slide, and staining with weak carbol-fuchsin. In the wet film, the large number of the organisms, their uniform character, and their very rapid rotatory movements, will lead one to suspect cholera; in the stained film, the characteristic comma-shaped vibrios and their 'fish in stream' arrangement will add to the suspicion. One additional method that might be considered within the scope of the clinician is the simple enrichment method with peptone water; a few loopfuls of stool are placed in alkaline peptone water, left overnight in tropical climates—or incubated at 37°C. for eight hours in cooler climates—and a loopful from the surface examined by the wet- and dry-film methods.

At least 50 per cent of mild cases of cholera, and a higher percentage of severe ones can be diagnosed in this way with a considerable degree of certainty, but the final identification of the vibrio will depend on more elaborate bacteriological methods.

Needless to say, whenever possible the help of a bacteriological laboratory should be obtained; an ounce of freshly passed cholera stool should be placed in a sterile wide-necked bottle, which must be corked and very carefully sealed if it is to be sent any distance, and then despatched with as little delay as possible to the laboratory. Some time will be saved if an inoculated peptone water tube is also sent. From a necropsy, a loop of intestine with its fluid contents should be tied off, cut out, and sent to the laboratory in a sterile jar.

Differential diagnosis.—Food poisoning (*e.g.* so-called ptomaine, or mushroom) and also acute arsenic poisoning are likely to simulate cholera. Some of the points of distinction are shown in tabular form below :—

TABLE IV
Differential diagnosis of cholera

	Cholera	Food poisoning	Arsenic (and antimony)
<i>Epidemiology</i> ..	Associated with other cases in neighbourhood.	Often single group of persons who shared meal.	Often one person only.
<i>Incubation</i> ..	24-72 hours	4-24 hours	½-2 hours.
<i>Onset</i> ..	With purging	With vomiting	With burning in throat followed by vomiting.
<i>Nausea and retching.</i>	None	Yes	Yes, retching marked.
<i>Vomiting</i> ..	Precipitate watery; rarely blood. Continuous.	Often single severe vomit; mucus, blood-streaked.	Violent, continuous mucus, often freely streaked with blood.
<i>Evacuation</i> ..	Early. Continuous pouring out of pints of watery fluid, inoffensive.	Frequent. Usually follows vomiting: faecal, <i>plus</i> blood and mucus, often offensive.	Delayed. Single massive followed by frequent passing blood and mucus.

TABLE IV—*contd.*

	Cholera	Food poisoning	Arsenic (and antimony)
<i>Tenesmus</i> ..	None	Yes	Very marked.
<i>Abdominal tenderness.</i>	None	Marked. All over abdomen.	Very marked.
<i>Dehydration</i> ..	Very marked	Distinct	Slight.
<i>Muscular cramps</i>	Constant and severe.	Less constant. Extremities only.	Severe.
<i>Surface temperature.</i>	Subnormal	Often up to 100-102°F.	Normal or subnormal.
<i>Headache</i> ..	None	Often	Often.
<i>Urine</i> ..	Suppressed	Seldom suppressed	Sometimes suppressed later.
<i>Blood</i> ..	Leucocytosis, mononuclear increase.	Normal	Slight leucocytosis. Normal differential.

Other conditions from which it will have to be distinguished are :—

(a) *Fulminant bacillary dysentery*; the diagnosis will be bacteriological but it is unnecessary to wait for this, as intravenous saline treatment is indicated in either case, though in a case of Shiga dysentery the early administration of anti-serum would probably improve the prognosis.

(b) *The algid and choleraic forms of malaria*; the differential diagnosis here is very important, for, though the administration of intravenous saline would do the malaria patient no harm and probably some good, the withholding of specific anti-malarial treatment might easily be fatal; if there is any doubt, a blood film should be examined immediately.

(c) *Trichinelliasis*; the acute gastro-intestinal onset of a heavy infection of *Trichinella spiralis* may simulate cholera, and later the muscular cramps might be a confusing element. The exclusion of this diagnosis will be difficult, and a positive diagnosis of cholera must be sought. This infection, however, is rare in India, the main home of cholera.

PREVENTION

Grand strategy.—No cholera pandemic has occurred since 1884, and in fact for the last thirty years the disease has been confined to its Asiatic homes and to other Asiatic countries in their immediate vicinity. This however has been achieved only by very elaborate quarantine organizations in a large number of countries and at a considerable cost, both directly to those countries which have to maintain these organizations, and indirectly to the shipping companies whose ships are very frequently delayed. Quarantine regulations are directed against other diseases besides cholera, but, nevertheless, cholera is probably the most important of all 'quarantinable' diseases. This matter therefore seemed a suitable subject for the League of Nations Health Organization to take up, and at a meeting of the Office Internationale d'Hygiene Publique in 1930, they drew the attention of the Indian representative to the fact that India was the main source of origin of previous pandemics, and suggested that investigations should be initiated

Prevention of epidemic extension.—In all countries there are strict quarantine regulations for all ships coming from infected ports, and certain large ports in the endemic areas, *e.g.* Calcutta, are more or less permanently classed as infected. The actual procedure and the measures taken vary in different countries, but in some cases the authorities have gone as far as to provide for anal swabs being taken from all the lower-class passengers. Pilgrim ships going to Mecca have been submitted to the strictest quarantine regulations, and these have included the inoculation of all pilgrims prior to embarkation.

Within countries, control measures are more difficult to carry out, and have on the whole been less successful, but during the last few decades special efforts have been made to prevent epidemic extension as a result of religious melas. At the sites of these melas, latrine arrangements, anti-fly measures and protected water supplies have been instituted. Provision has been made for the immediate treating and isolation of the sick. Similar arrangements have been made at various points on the roads and railways leading to and from these melas, and during the last few years, systematic inoculation of pilgrims has been carried out. Besides these special precautions in connection with melas, at the height of the epidemic seasons, provision is made at the large railway stations for detaining and detaining in the railway hospital any passenger showing suspicious symptoms. Epidemic staffs are employed for visiting any village where a case has been reported; medical aid is given to the sick, disinfection of the water supplies carried out, and often inoculation of the whole community undertaken. Attempts are also made to control the movement of the population to prevent extension of the epidemic to other villages.

In the matter of disinfecting wells, discrimination should be observed and only suspected sources of infection treated at first, for, if all well water is made undrinkable, the inhabitants will be compelled to find other waters which may be even more contaminated: *vide infra* chlorination of water supplies.

Control in the endemic areas.—Here the public health policy to be adopted is somewhat different from the above. One of the main differences is that all measures should as far as possible be of a permanent nature, and, further, should be in force practically the whole year.

If all the inhabitants of these areas could be provided with a protected water supply, it seems very probable that cholera could be stamped out (*see footnote on water supplies**). Though the habit of indiscriminate

***Water supplies.**—A local water supply from wells depends upon the depth of the water table and character of the water-bearing soil, sand and gravel, of course, being ideal. Although a deep tube well 750–1,000 feet should be able to produce water of greater quantity, and perhaps of greater potability, such wells are expensive, and in nearly all parts of the Ganges alluvial plain, for example, shallow tube wells, 30 to 150 feet deep, will yield sufficient water for a household. The depth will vary, as it is

defaecation in the open fields around the village that is general in most Indian villages probably helps to spread infection during exacerbations of endemic cholera, it is almost certainly not the main factor, except that it may lead to the contamination of water supplies, for there is little evidence of correlation between the fly population curve and cholera incidence in the endemic areas in India.

Another important measure is making arrangements for the immediate isolation and treatment of all recognized cases, and the segregation of contacts. Some form of compulsory notification is an essential prelude to this. Inoculation is practised as a palliative measure in the endemic areas, but it is unlikely to achieve success and, in the writer's opinion, is not to be recommended, because, though it may prevent the full development of symptoms, it is unlikely to preclude infection completely; such an infection, which will result in the passage of virulent vibrios for a few days, by an unsuspected individual, is a greater source of danger than a frank case of cholera.

In some endemic areas, widespread bacteriophage treatment of water supplies has been carried out, with questionable success.

Control in hospitals or institutions.—The sick and contacts should be isolated; any suspected water supply should be disinfected; special measures should be taken to add a strong disinfectant, *e.g.* chloride of lime, immediately to all stools and vomitus, and to allow it to act for a sufficient time to destroy all the vibrios before the stool is allowed to pass into the common drain; all linen from the patients should be placed in disinfectant; the clothes of the attendants should be discarded when they leave the ward and these should likewise be placed in disinfectant; the staff should not be allowed to take any food on the premises or to smoke; flies should be excluded rigidly from the wards and latrines; and all those who come in contact with cholera patients should be inoculated, preferably a week or more before they come on duty in the cholera wards, but otherwise at the earliest date possible. There is little evidence of a negative phase.

Personal prophylaxis.—Inoculation causes little or no reaction and is therefore worth having done once every year, at least. All water and milk must be boiled, and uncooked vegetables avoided; no soda water or ice should be used unless it is known to have been made from boiled water; and no cut fruit or food cooked the previous night and left standing should be eaten. These are the standard rules to avoid bowel disease. They should always be

necessary for the well strainer to be in a sand stratum which is below the water-table height during the dry season. The water, although hard, is usually of high purity.

Open wells have a greater yield than shallow tube wells in that they also serve as a reservoir. However, it is harder to maintain purity even when the wells are protected by a proper apron and parapet wall. The purity can be maintained if the well is covered and a pump installed.

When the water supply is from a *doba*, or stream, it must be pumped into a reservoir, where proper disinfection can be carried out.

There is still a mistaken idea of the danger of sub-soil pollution of a well. Nearly all well pollution is from the surface. In a limestone formation, or where there are fissured rock formations, pollution may travel quite long distances, but in other formations the extension of pollution from a source depends upon the texture of the soil, the height of the water table, the slope of the water table, and the direction of the flow.

The old theory that a well must be 50 or 100 feet from a latrine is incorrect. In rare cases, the pollution may travel 400 feet and in others only 5 feet. In the Southern United States, Caldwell found that the *Bacillus coli* travelled a little over 10 feet in the direction of flow. Dyer (1941) found that, in the Punjab, *B. coli* only travelled a little over 15 feet in 9 months, and in Bengal, 5 feet in 8 months. Therefore, in planning a latrine it should be below the well. The direction of the ground water flow can be roughly estimated by the topography of the ground.

in this country with a view to stamping out the disease in the endemic areas.

In 1931, the Indian Research Fund Association made cholera one of their main subjects of research, with some of the results reported above. The Indian workers, in collaboration with others in England, established the identity of the true cholera vibrio, showed that the cholera case was the only source of infection, and defined the true endemic areas in India; thereby they opened the way for a definite policy of control. This policy, which is a long-term one, consists in a sustained sanitary drive in the true endemic areas. This will be expensive, and it is hoped that, as all provinces in India will benefit by any results, assistance will be given to those provinces in which the endemic areas exist.

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followed in the tropics, but they must be observed with religious formality during a cholera epidemic. There is little danger of direct infection of personal attendants on the sick, provided that they avoid a precipitate vomitus splashing into their faces, and never take food on the premises or until they have changed their clothes and washed their hands.

Special measures of prevention

Inoculation.—Haffkine, who was a student of Pasteur, carried out experiments in Paris in 1892 and applied them in India. He used live avirulent cultures followed by virulent cultures. Kolle showed that killed cultures were equally efficacious, and killed cultures have been used since. Cholera vaccine has been used very widely for a quarter of a century. Recent evidence of its value rests mainly on one statistically designed and executed investigation conducted under the auspices of the Indian Research Fund Association (Russell, 1927). The figures were as follows :—

		Persons	Cases	Deaths
Two doses of vaccine by injection	..	8,485	31	2
Three doses of oral vaccine	..	4,982	18	4
Controls	..	40,258	711	277

It is usual to give two doses, but in many wholesale inoculation schemes it has only been practicable to give one, and the results have not been much inferior. This fact, and the apparent equal success of the oral vaccine, about which many workers are very doubtful, has led the sceptics to question the value of cholera vaccine altogether.

The vaccine should be prepared from recently isolated strains of non-hæmolytic O-sub-group-I cholera vibrios. The vaccine should contain 1,000 million organisms per c.cm. and the usual dose is 1 c.cm., followed a week later by a second dose, of 2 c.cm.

Immunity is said to last from 3 to 6 months, and there does not appear to be a negative phase.

Oral vaccine. Besredka's oral bilivaccine has been used more extensively in cholera than in any other disease. Its value was investigated by Russell (*loc. cit.*) who reported favourably on it (*vide supra*).

Bacteriophage.—In Bihar and Assam, extensive trials were carried out in which bacteriophage was distributed for the treatment of their water supplies to a large number of villages in the areas where cholera occurs frequently. The results appeared satisfactory, but would not survive statistical criticism. In later years, the trials were repeated with disappointing results.

Disinfection of water supplies. Chlorination.—For filtered water supplies, the usual rule is one part in five million, that is one part of chlorine, or if the chlorine content of the bleaching powder is $33\frac{1}{3}$ per cent, 3 parts of bleaching powder; this works out at 6 lb. of bleaching powder per million gallons of water. But, as the chlorine content of bleaching powder varies from sample to sample, and as the chlorine fixing power of different water supplies also varies, no rule of thumb can be adopted and the amount to be added must be calculated for each well or cistern.

The following is a standard method of calculating the amount of bleaching powder to be added.

Three standard solutions made with distilled water are necessary:

(a) 1 in 1,000 solution of the bleaching powder to be used.

(b) 10 per cent potassium iodide solution.

(c) 1 per cent starch solution.

The volume of water to be chlorinated must first be ascertained. For wells, this can be calculated from the depth of the water and the diameter of the well; by the formula $\pi r^2 \times \text{depth}$, where r is the radius (half the diameter) of the well. The capacity of tanks and cisterns is calculated by multiplying the length

by the breadth by the depth of the water. One cubic foot of water is equivalent to $6\frac{1}{4}$ gallons.

Example. A well is 10 feet deep and has a diameter of 6 feet. Therefore it contains $\pi r^2 \times 10 \times 6\frac{1}{4} = 2\frac{1}{2} \times 9 \times 10 \times 2\frac{1}{4} = 1,768$ gallons.

Take five white bowls or flasks and in each place 500 c.cm. of water to be treated.

Take a clean graduated 1 c.cm. pipette, and wash it thoroughly with distilled water. With this pipette add varying quantities of the 1 in 1,000 bleaching powder solution to the water in the five vessels, 0.5 c.cm., 0.7 c.cm., 0.9 c.cm., 1.1 c.cm., and 1.3 c.cm. to the first, second, third, fourth and fifth bowl, respectively.

Stir the mixture in each bowl with a clean glass rod, beginning with the bowl containing the least amount of chlorine solution, and going to the one containing the next smallest, and so on.

Allow them to stand for at least an hour. Then test for free chlorine by adding to each bowl about 1 c.cm. of 10 per cent potassium iodide solution and 1 c.cm. of freshly prepared starch solution. Mix well and note the first bowl that gives a faint blue colour. Note the amount of bleaching powder solution that was added to that particular bowl and multiply by 20. The result gives the number of pounds of bleaching powder required for one million gallons of water; to this figure add 3 lb. which, if the bleaching powder is approximately 30 per cent, is the usual safety margin allowed for one million gallons of water. Now calculate the amount of bleaching powder that should be added for the amount of water already ascertained to be present in the well or cistern that is to be chlorinated.

For example, say the third bowl is the first to give the faint blue colour; then $0.9 \times 20 = 18$ lb.; and 3 lb., making 21 lb.

In the case of the hypothetical well mentioned above which contained 1,768 gallons of water, the amount of bleaching powder required would be :

$$\begin{aligned} &1,000,000 \\ &= 0.037128 \text{ lb.} \\ &= 260 \text{ grains (or about 17 grammes).} \end{aligned}$$

Alternative method. If centimetre pipettes are not available, a rough method of titrating may be adopted, as follows :—

Place a pint of water in each of the 5 bowls, and add 10, 15, 20, 25, 30, drops, respectively, of bleaching powder solution from a dropper; stir very thoroughly, as explained above, and after the usual interval add the potassium iodide and starch solutions.

The calculation is made as follows :

$$\begin{array}{l} \text{Minimum number of drops of} \\ \text{bleaching powder solution added to} \\ \text{the first bowl in which the blue} \\ \text{colour was distinct.} \end{array} \times 0.44 + 0.021 = \begin{array}{l} \text{Grains per gallon of} \\ \text{water to be treated.} \end{array}$$

Number of drops from the dropper
that make a drachm.

Example. If the fourth bowl was the first to give the blue colour, then
 $33 \times 0.44 + 0.021 = 0.1585$ grains per gallon
 $= 158$ grains per 1,000 gallons.

or, in the case of the example given above,
 $\frac{1}{10} \times 158 = 280$ grains (or about 18 grammes).

Potassium permanganate.—This has been a very popular disinfectant for wells. Its main advantage lies in its extreme simplicity of application : its action on cholera vibrios in high dilution appears to be specific. The usual criterion of adding permanganate, namely, until the water is a slight pink colour is not a safe one, if there are likely to be other faecal pathogens present. A dilution of 1 in 500,000, which produces a faint purple colour in filtered water, kills cholera vibrios in a very short time, but it will not kill all coliform organisms even in 24 hours.

This dilution is obtained by adding $\frac{1}{4}$ th grain of permanganate to each gallon of water, or roughly one pound to each 50,000 gallons.

In our hypothetical well, which contained 1,768 gallons, the amount of permanganate required would be a little over half an ounce.

Neither the permanganate nor the bleaching powder should be thrown into the well, but should be mixed in a bucket, the supernatant fluid being

poured off and renewed until the whole amount has gone into solution. Then, the water in the well should be thoroughly mixed by repeatedly lowering and raising the bucket.

TREATMENT

Historical.—Charms, amulets and magic were credited with playing important parts in the treatment of cholera during the last century, and they still held their own even at the beginning of this, amongst less educated communities. This is not surprising, as the methods of treatment of cholera that were employed by the practitioners of scientific medicine during the whole of last century were scarcely better. The earliest drugs that were used include calomel, a drug that appears to have been predominant at all periods and is still in use, in doses of 1 to 2 grains every quarter of an hour until the patient recovered—or, which was more frequently the case, died—opium, *Cannabis indica*, sulphuric and nitrous acids, quinine, strychnine, arsenic, iron, and in fact almost every drug in the pharmacopœia, and many that were not in it. The multiplicity of drugs suggests very strongly that none was of any real value. Other methods employed were venesection, blistering, cupping, wrapping in cold sheets, hot baths, 'electro-magnetic insulation', and a number of other procedures.

With the advent of bacteriology and Koch's discovery of the vibrio, the intestinal antiseptics naturally had a phase, but the value of none was established.

Saline injections were used nearly a hundred years ago in England. The immediate result was said usually to be good; but as emphasis is laid on the word *immediate*, one must assume that the final results were disappointing, and this assumption is strengthened by the fact that this method of treatment was abandoned. Intravenous injection of saline was used in Shanghai in 1875 and in India between 1906 and 1908; there is little evidence that it materially affected the appalling prognosis in this disease. The following year Rogers introduced his hypertonic saline; this constituted the first really decisive advance in the treatment of cholera, and the last thirty odd years has seen very little change in the standard treatment which remains much as he formulated it. If the results of treatment are now better than they were thirty years ago, it is because the technique is better understood and more promptly put into operation.

Introduction.—Treatment must be considered under three headings :—

A. *Specific.*

B. *Maintenance of biochemical equilibrium.*

C. *Symptomatic.*

Hitherto the failure of specific treatment has led to an emphasis on the other two aspects of treatment. The complete success of efficient biochemical-maintenance treatment in a large percentage of cases indicates that, even in those cases in which the natural immunity fails to prevent the establishment of infection, immunity is rapidly developed and soon overcomes the infection. Nevertheless, it is obvious that if the infection could be overcome and/or its 'toxin' neutralized earlier, the treatment to maintain biochemical balance might be reduced, or even omitted in some cases, without endangering the life of the patient.

A. **Specific treatment.**—There are two objectives :—

(i) **The destruction of the vibrio.**—All the various intestinal antiseptics that have been used in the past have failed to influence the course of the disease in the case of cholera.

The advocates of **bacteriophage** have claimed an earlier disappearance of the vibrios after 'phage administration.

Bacteriophage should not be given to the exclusion of other treatment, but in addition to it; no other 'specific' should, however, be given by mouth with the 'phage. A good 'phage, active against the local strain of cholera, is essential. One ampoule containing about 3 c.cm. of 'phage is given every two hours, or large doses at longer intervals for at least two days.

The **essential-oils mixture** that has been advocated by some workers is presumably supposed to act as a disinfectant. The essential-oils mixture consists of :—

R. Olei caryophilli	} ℥v
„ cajuputi	
„ juniperi	
Acidi sulphurici dil.	℥xv
Spiritus ætheris	℥xxx

Half a drachm of the mixture is given in an ounce of water every 15 minutes, up to a maximum of 16 doses.

It is not a treatment that the writer can recommend except as a gesture of despair when no other treatment is available.

The advent of the sulphanilamides has once more raised our hopes of finding a drug that will act directly on the vibrio, and the recent success with **sulphanilyl-guanidine** has suggested that the long-sought specific may possibly be a drug of this class, of which the bacteriocidal and bacteriostatic properties are high and the absorption coefficient low.

Sulphanilyl-guanidine is tolerated in very large doses. The dose recommended is 0.1 gm. per kilogramme of body-weight immediately followed by 0.05 gm. every four hours. This is to say, a patient of moderate size, 50 kilogrammes or 110 pounds, should receive an initial dose of 5 grammes followed by 2.5 grammes every four hours until symptoms subside. Up to date, our experience in Calcutta has been very promising; in a series of over sixty cases in which this dosage was given, we have lost no case, against a death rate of about 6 per cent amongst patients treated with saline infusions only (Napier *et al.*: in press). Reports from elsewhere have not been so satisfactory.

(ii) **The neutralization of the toxin.**—No great success has been achieved in this direction. Potassium permanganate has been most disappointing in the writer's experience, and, in the large doses advocated, it appears to cause gastro-intestinal irritation very frequently. It seems very questionable whether its *in vitro* toxin-oxidizing properties are reproduced *in vivo*. The dose recommended is two enteric-coated pills, of 2 grains each, every 15 minutes for the first two hours, and then every half hour until the acute symptoms have subsided or 80 pills have been taken.

Kaolin as an adsorbent has also been very disappointing; the dose recommended is one pound in a pint of water, to be taken *ad lib*.

B. The maintenance of biochemical equilibrium.—The objectives are :—

- (i) *the replacement of fluid,*
- (ii) *the maintenance of the blood and tissue chlorides at their normal level, and*
- (iii) *the counteraction of acidosis.*

All three can be achieved by suitable intravenous therapy, for example, by the hypertonic and alkaline saline treatment recommended by Rogers. The procedure that he suggested was as follows :—

Rogers' treatment—Two solutions are prepared :—

- (a) the hypertonic saline consisting of
sodium chloride—120 grains,
calcium chloride—4 grains,
pure, or distilled, water up to a pint,

this solution is autoclaved or boiled to ensure sterility;

- (b) the alkaline saline which is prepared as follows :—
sodium chloride—90 grains,
pure, or distilled, water 1 pint;

this solution is autoclaved to ensure sterility, and to it is added, from a previously sterilized packet containing the exact amount, 160 grains of bicarbonate of soda*.

* Sodium bicarbonate is converted to carbonate if a solution of it is heated for any length of time.

He took as his main indication for the giving of intravenous saline the specific gravity of the blood, measured by means of glycerine bottles (*vide supra*). A specific gravity of 1061, he suggested, indicated a loss of one pint of fluid, 1062 two pints, 1063 three pints, and so on. Fluid was replaced accordingly, by giving first one pint of alkaline saline and making up the balance with hypertonic saline. He recommended giving the intravenous salines at the rate of about a pint in 5 minutes.

Rogers' treatment has been the basis of all successful treatments of cholera for the last 25 years. During this time many modifications have been introduced, and individual workers have naturally interpreted his technique in different ways.

Modified procedure.—In the cholera wards of the Campbell Hospital in Calcutta, the procedure is as given below; this scheme has been worked out by the physicians, especially Dr. B. C. Chatterjee, attached to this hospital, in conjunction with the cholera research workers at the Calcutta School of Tropical Medicine. The following four solutions are made up and kept ready for use. They are made with pyrogen-free* sterile distilled water, and the precautions suggested above regarding the sterilization of bicarbonate in the dry state are observed.

(a) *Hypertonic saline.*

Sodium chloride	140 grains
Pyrogen-free distilled water	1 pint

(b) *Alkaline saline.*

Sodium chloride	90 grains
" bicarbonate	180 "
Pyrogen-free distilled water	1 pint

(c) *Alkaline hypotonic saline.*

Sodium chloride	60 grains
" bicarbonate	180 "
Pyrogen-free distilled water	1 pint

(d) *Bicarbonate solution (5 per cent).*

Sodium bicarbonate	440 grains
Pyrogen-free distilled water	1 pint

Indications.—Intravenous solutions are given in all severe cases in which there is any evidence of dehydration, or if the patient is at all collapsed; if possible, the extent of this dehydration and collapse are

* Pyrogens are protein substances mainly derived from bacteria; they are found in waters distilled in ordinary open vessels, or left standing after distillation. Subsequent sterilization does not destroy the pyrogens. Pyrogen-free water is prepared as follows:—

In a clean glass still, re-distil some freshly distilled water to which a little sulphuric acid and one or two crystals of potassium permanganate have been added to give it a faint pink colour. If, during the process of distillation, the pink colour disappears from the water in the still, a little more sulphuric acid and potassium permanganate must be added.

The distillate is collected in a closed glass flask which has been previously prepared by rinsing first with a solution of potassium bichromate and sulphuric acid, then washed out, first with distilled water and then with pyrogen-free water, and finally sterilized by autoclaving.

The pyrogen-free water is sterilized in an autoclave, and may be used for about 3 to 4 days.

When distilled water is already available, the following method may be adopted to ensure that it is pyrogen-free:

Add powdered charcoal (B.D.H. activated charcoal for preference) to distilled water in the proportion of 1 gramme to a litre. This is shaken thoroughly for a few minutes and then put aside for the charcoal to settle out; the supernatant fluid is passed through filter paper into a scrupulously clean flask or bottle (*vide supra*). The flask or bottle must not be plugged with cotton-wool but closed with a glass stopper or covered with paper, which is tied round the neck of the receptacle; it must then be autoclaved or boiled immediately, after which it may be stored for a few days, but, if it is not used within a week, it must be treated again.

ascertained by estimating the specific gravity of the blood and taking the blood pressure. If the systolic blood pressure is below 80 mm. of mercury, or the specific gravity of the blood 1058 to 1060, $1\frac{1}{2}$ pints are prescribed, if 1060 to 1062, two to $2\frac{1}{2}$ pints, and if 1062 to 1064, up to three pints. It is seldom wise to give more than three pints in the first instance, at any rate in the low-weight type of Indian, but, if circumstances permit, the perfusion should be continued by the drip-feed method.

Method.—The specific gravity of the blood is estimated under clinical conditions by adding drops of blood to a series of bottles of glycerine diluted with distilled water to make the specific gravities 1050, 1052, 1054 and so on, up to 1070; for practical purposes, it is usually sufficient to have bottles from 1054 to 1064. If the specific gravity of the blood is greater than that of the glycerine in the bottle, the drop will sink; if it is less, it will come to the surface. The bottles can be used for some time if they are carefully corked; if they are not kept closed, the glycerine will absorb moisture from the atmosphere and the specific gravity will fall, in the humid climate of the endemic areas, or will rise as a result of evaporation in the drier climates.

Technique.—Blood is taken from the finger or ear into a Wright's pipette. The tip of this is placed just below the surface of the glycerine in the bottle of the highest specific gravity, and a small drop is squeezed out which will probably rise to the surface. This is repeated in each bottle until the extruded drop either remains stationary or falls to the bottom of the bottle. The specific gravity of the bottle in which it remained stationary is the specific gravity of the blood. If it rises in one and falls in the next, the specific gravity may be taken as between these two.

As dehydration and loss of chlorides are the first pathological processes to be counteracted, hypertonic saline and alkaline saline should be given in the proportions 2 to 1 within the first 24 hours of onset. Later, acidosis develops, and during the next 24 hours, that is, from 24 to 48 hours from the onset, the proportions should be reversed, and 1 part of hypertonic saline with 2 parts of alkaline saline given. After 48 hours, acidosis will probably be the most prominent feature, and hypotonic alkaline saline should be given. If however the specific gravity of the blood is not much increased, but nevertheless the patient is suffering from acidosis, then the bicarbonate solution only is required, and about half a pint of this should be given.

It will very often be necessary to repeat the infusions, sometimes as many as half a dozen times, if the fluid evacuation continues, if the patient collapses again, or if the dehydration is re-established (evidenced by a rise in the blood specific gravity).

Recent work on shock suggests that human serum or plasma is likely to remain longer in the circulation than the saline infusions, and the procedure of running in two pints of hypertonic saline and following this by a pint of plasma to keep it there, so to speak, has been adopted in a few cases, apparently with complete success, but, as it will be seen from figure 119, there are not the same indications for giving plasma in cholera as in shock.

Apparatus and technique. Fluid may be introduced into a vein directly, or by the open method. The special apparatus required includes a graduated glass reservoir with at least six feet of rubber tubing attached, in the length of which a drip-feed apparatus may be interposed a foot below the reservoir,

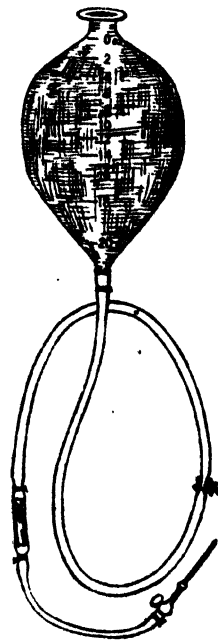


Figure 121: Apparatus for giving saline, with the drip-feed apparatus incorporated in the tube (in this figure the length of the tubing between the drip-feed and the needle is shorter than it would be in practice).

and 3 inches of glass tubing to act as a 'window' a short way from the lower end. At the lower end of the tube, a record needle adapter, preferably with a stop-cock, is inserted, and a serum syringe needle fitted (see figure 121). For giving by the open method, the needle adapter is replaced by a special intravenous cannula, again preferably with a stop-cock (see figure 122).

A suitable vein, usually in the ante-cubital fossa, is chosen; failing this, a vein in front of the internal malleolus or even on the dorsum of the hand may be used.

The patient is placed in the recumbent position under a good light; the whole of the arm is exposed and is supported at a convenient angle with the body, in complete extension, with the palm upwards, resting on a pad placed under the elbow; and the operator sits facing the elbow.

A sphygmomanometer cuff or a tourniquet is applied to the arm; compression of the deeper arterial supply is avoided; if necessary, the patient should be made to open and close the hand, or to bend and extend the elbow, several times in order to fill the veins.

The selected area is painted with tincture of iodine, and then washed with alcohol. Local anæsthesia of the skin may be produced by injecting a few drops of 2 per cent novocain solution (or some suitable substitute) with a fine hypodermic needle, to form a weal over the selected vein. The arm must be held firmly, so that the patient cannot pull it away or move it.

Next, with all aseptic precautions, a needle, connected with the infusion apparatus is filled with saline solution so that all the air is expelled. The needle must be sharp and have a short bevel. It is then held at a very acute angle with the point touching the skin and is thrust through the skin into the vein. Some workers prefer to make a preliminary nick in the skin. To the experienced hand, the entrance of the needle point into the vein is indicated by a sudden failure of resistance. The reservoir should be held by an assistant at about, or just below, the level of the patient, so that when the stop-cock is opened, blood will flow into the tube and be visible at the window. The tourniquet is now released and the reservoir raised, and the flow will be reversed. The reservoir should be attached to a stand, about 3 to 4 feet above the level of the patient.

A very convenient refinement is a serum syringe with a side nozzle to which the lower end of the tubing from the reservoir is attached, the adapter being discarded; the needle is attached in the usual position. With the aid of this syringe, the operator has perfect control of the needle whilst inserting it into the vein. The piston is slowly withdrawn, when blood will appear. The tourniquet is released, and the side stop-cock opened to allow the saline to flow.



Figure 122 : Cannula for inserting into vein.

When the veins are collapsed, the open method is employed. A tourniquet is applied as before. Under a local anæsthetic a small incision is made, the skin being steadied by the index finger and thumb of the left hand. The vein is isolated by forceps dissection. The closed forceps, or an aneurysm needle, are then passed under the vein, and a double strand of sterilized catgut is drawn

under it. The catgut is divided to provide two ligatures. The distal piece is drawn down under the exposed vein and is tied, the ends being left long. The proximal one is drawn up under the vein to the upper end of the wound.

The fluid is now allowed to flow through the cannula until all air is expelled*. The vein being steadied by the lower ligature, a nick is made into it with a pair of fine scissors. The cannula is inserted into the vein, the other ligature being single-knotted and drawn around the vein with the cannula inside. The flow of saline is then started.

When the infusion is completed, the cannula is withdrawn, but the ligature is not knotted or cut, in case a later transfusion is required; the wound is closed temporarily with a single stitch, and a light dressing is applied.

A modification of this method is to use a needle, as in the direct method, and to push the needle into the exposed vein. Afterwards, the needle is withdrawn and the wound is not closed, but simply dressed, so that the same vein may be used again.

Rate and temperature of administration.—At first, while the patient is pulseless, the infusion can be given briskly, at about 4 ounces per minute,

* As bicarbonate solution will cause pain and a sharp local reaction if even a small amount is allowed into the subcutaneous tissues, a small amount of isotonic saline should always be placed in the reservoir first, until the cannula is *in situ* and a satisfactory flow has started.

but, when the pulse recovers or the patient complains of an oppressive pain in the chest, the rate should be decreased considerably and the remaining infusion given at the rate of about a pint in 15 to 20 minutes. If the pain or feeling of oppression in the chest returns, or if there is a very severe headache, it may be necessary to reduce the rate still further. Rigors may interfere with the giving of the infusions, but if pyrogen-free water is used, these will be much less frequent. These difficulties should as far as possible be met by reducing the rate of flow rather than by abandoning the procedure. After three pints have been given, the infusion may be continued at a very much slower rate, 40 or even 20 drops per minute (1 pint in four or eight hours).

If the rectal temperature is 101°F. or above, all intravenous infusions should be given with caution, as a sharp reaction possibly ending in hyperpyrexia is likely to occur. The temperature of the fluid must certainly not be higher than room temperature. If the rectal temperature is also low, it may be advisable to warm the saline up to body temperature, especially in cold climates, but in the hot weather in most endemic areas this is a very unnecessary complication of administration.

Other routes of administration.—In children and when it is not possible to find a vein, hypertonic saline may be administered subcutaneously, intramuscularly, into the sternum or tibia, or into the peritoneal cavity; alkaline saline cannot be given by these routes. In mild cases, alkaline isotonic saline can be given per rectum, but if there is much purging, little will be absorbed. After administration of salines intraperitoneally, the foot of the bed must be raised as the absorption from the pelvic peritoneum is very poor.

C. Symptomatic treatment.—The intravenous therapy will play an all-important part in the treatment and prevention of collapse, and of many other serious complications, such as anuria, but other measures may also have to be adopted.

Collapse and shock.—The administration of atropine sulphate 1/75th grain when the patient is first seen, to be repeated after about 12 hours if the patient is still collapsed, was first suggested by Lauder Brunton and is recommended by Rogers. Atropine reduces all secretions, except renal secretion, it therefore helps to conserve fluid and at the same time to reduce the tendency to oedema of the lung when saline is given. It also reduces irregular peristalsis, and is a cardiac stimulant. This appears to have some effect in reducing the shock. Pitressin 1 c.cm. (pituitary extract—posterior lobe) or, if not available, disoxycorticosterone acetate 20 c.cm. (synthetic suprarenal cortical extract) will often help towards the recovery of the pulse during the collapse stage. Other routine measures for the treatment of shock, hot water bottles, massages, etc., may have to be resorted to.

Anuria.—With the recovery of the blood pressure, the kidneys will usually start to secrete urine again, but if hypertonic saline, alkaline saline, bicarbonate solution, and injections of pitressin and disoxycorticosterone acetate fail, glucose 5 per cent (1 pint), intravenously, strophanthin gr. 1/100, caffeine and sodium benzoate gr. iv intramuscularly, hot fomentations to the loins, dry cupping, hot colonic washes, intravenous sodium sulphate (1.89 per cent) by the drip-feed method, and finally distension of the bladder with warm citrate saline (2 per cent citrate in normal saline) should be tried in succession. Injections of salyrgan 1 c.cm. have been reported on very favourably in a few cases.

When once re-established a careful watch should be kept on the urinary output, and if it falls below 1 pint in 12 hours, the various measures should be repeated.

In the reaction stage there may be hyperpyrexia; this should be treated very cautiously with hydrotherapy.

Vomiting and hiccough may be persistent and are very tiring; this will often be relieved by a belladonna plaster, or, it will respond to $\frac{1}{4}$ -gr. doses of calomel repeated at half-hour intervals up to six doses, followed by a dose of bismuth salicylate. The following prescription will be found useful :—

R Calomel	gr. $\frac{1}{4}$
Chloretone	gr. 2
Menthol	gr. $\frac{1}{4}$
Sodium bicarbonate	gr. 2 $\frac{1}{2}$

Muscular cramps should respond to the hypertonic saline treatment, but, if they persist and are very painful, self-administered whiffs of chloroform will often meet the case.

Morphia and alcohol should be avoided at all stages of the disease. Rogers considered that the early administration of morphia definitely affected the later prognosis, making both suppression and acidosis much more likely to occur.

Diet and nursing.—As the disease is a short one, diet can be reduced to a minimum. The patient should have at hand a free supply of glucose water flavoured with lime, or barley water. If it is obtainable, *dab* (green coconut water) will probably be the best drink. If glucose is not retained by the stomach, or the rectum, it should be given intravenously as a 5 per cent solution, up to a pint.

Later, arrowroot, albumin water, milk whey, milk, fruit juices, meat extract, and lightly boiled eggs may be added gradually. The hydrochloric acid content of the gastric juice is always low, so that a mixture containing dilute hydrochloric acid and pepsin may help the digestion. In a week or so, the patient may be allowed to return to a full diet.

Careful nursing will be very necessary to save the patient from exhaustion in the early stages of the attack, and later a careful watch for returning anuria and other complications will have to be kept. During convalescence great care must be taken not to allow the patient to do too much for himself, as sudden heart failure is not uncommon. However, on the whole, convalescence is very rapid, once the acute symptoms have subsided.

Summary of treatment.—The fate of the patient will depend on the skill of the physician, on the facilities that the latter has at his disposal, and on the energy that he devotes to the case. Of the 'specific' treatments, only cholera-phage and sulphanilyl-guanidine in large doses are worth trying; they should not be used together. Neither of these should be used to the exclusion of the intravenous infusion treatment, which will nearly always be necessary in a bad case, though it is probable that, if they are successful, they will reduce the necessity for, or the duration of, the infusion treatment. Therefore, as a routine, intravenous infusion of saline, as indicated above, should be immediately instituted, and $\frac{1}{75}$ th grain of atropine sulphate given. The symptomatic treatment must be given as the condition of the patient indicates. Convalescence should not be hurried.

Some reported results.—In 1936, Pasricha, deMonte and O'Flynn carried out a large series of treatments to appraise the value of cholera-phage in the treatment of cholera; the crude results were as follows :—

	Treated with 'phage	Treated without 'phage
Total number of cases	684	685
Total deaths	92	114
Percentage mortality	13.5	16.6

Further analysis of the data suggested that the difference between the 'phage-treated cases and the others was greater than the crude figures indicated.

In a second series, three years later, Pasricha, deMonte, Chatterjee and Mian (1939) compared a number of forms of treatment. After excluding all patients who died within three hours of admission, and the very old and very young, the results were as follows :—

Treatment	Number of patients	Number of deaths	Percentage mortality
Calomel ..	75	9	12.0
Potassium permanganate	35	4	10.8
Essential oils ..	46	4	8.7
Sulphapyridine ..	43	4	9.3
Choleraphage ..	43	1	2.3
	244	22	9.0

In this series the 'phage was prepared by a different method. The cases were taken strictly in rotation, but by a mistake, two patients were put on calomel to each one put on each of the other treatments.

In 1941, Chopra, deMonte, Gupta and Chatterjee reported the results of treatment with small doses of sulphanilyl-guanidine as follows :—

	Number of patients	Number of deaths	Percentage mortality
Sulphanilyl-guanidine	468	26	5.56
Controls	87	6	6.90

If only bacteriologically-proven cases were taken, the results were more in favour of sulphanilyl-guanidine. The dosages of sulphanilyl-guanidine in this series were very small; later they were increased, but were still far below the maximum safe dosage. It is significant that the percentage recovery rate was higher with the large dosage.

Conclusion.—In all these series, all the patients were subjected to the routine saline infusion treatment. The results appear to indicate that choleraphage has a definite beneficial effect. They also indicate a progressive improvement in the routine treatment for cholera in the hospital in which this was carried out, or possibly a decrease in the virulence of the disease; there is little external evidence to support the latter interpretation.

PROGNOSIS

This is intimately associated with treatment and the reader is referred to the previous paragraphs.

Prior to the introduction of the saline infusion treatment, the reported death rate was usually above 60 per cent ; in the decade ending 1908, Rogers reports the deaths as 54.2 per cent amongst Indian troops, 62.3 per cent in jails, and 78.5 per cent in the British army. In the early days of this treatment, it was reduced to about 20 per cent. Rogers quotes 20.8 per cent in Calcutta hospitals from 1915–1919 under his personal supervision. Under

sub-ideal hospital conditions at the present day, it is seldom above 10 per cent. It must be remembered that results of treatment in hospital will *always* be better than in the 'field', because in the worst cases, death occurs before the patient can reach hospital, and therefore not only are conditions better, but the population is a selected one.

REFERENCES

- BANERJEE, D. N. (1941) .. Hypochloræmia in Cholera. *Indian Med. Gaz.*, **76**, 345.
- CHATTERJEE, D. N., and MALIK, K. S. (1938). The Bacteriological Examination and the Hydrogen-Ion Concentration of the Urine of a Series of 122 Cholera Patients. *Indian Med. Gaz.*, **73**, 612.
- CHOPRA, R. N., DEMONTE, A. J. H., GUPTA, S. K., and CHATTERJEE, B. C. (1941). Sulphanilylguanidine in Cholera. *Indian Med. Gaz.*, **76**, 712.
- DEMONTE, A. J. H., and GUPTA, S. K. (1941). Erythrocyte Sedimentation Rate in Cholera. *Indian Med. Gaz.*, **76**, 213.
- DYER, B. R. (1941) .. Studies of Ground Water Pollution in an Alkaline Alluvium Soil. *Indian J. Med. Res.*, **29**, 867.
- GARDNER, A. D., and VENKATRAMAN, K. V. (1935). The Antigens of the Cholera Group of Vibrios. *J. Hyg.*, **35**, 262.
- LAL, R. B., RAJA, K. C. K. E., and SWAROOP, S. (1941). Statistical Enquiry into the Epidemiology of Cholera in Bengal. *Indian J. Med. Res.*, **29**, 425.
- NAPIER, L. E., and GUPTA, S. K. (1942). Survival of *Vibrio cholerae* in Gastric Juice. *Indian Med. Gaz.*, **77**, 717.
- PASRICHA, C. L., DEMONTE, A. J. H., CHATTERJEE, B. C., and MIAN, A. S. (1939). Treatment of Cholera (A Note on the Results of Treatment by Different Methods). *Indian Med. Gaz.*, **74**, 400.
- PASRICHA, C. L., DEMONTE, A. J. H., and O'FLYNN, E. G. (1936). Bacteriophage in the Treatment of Cholera. *Indian Med. Gaz.*, **71**, 61.
- ROGERS, L. (1911) .. *Cholera and Its Treatment*. Henry Frowde and Hodder and Stoughton, London.
- Idem* (1933) .. Notes on Making Epidemic Forecasts. *Indian Med. Gaz.*, **68**, 125.
- RUSSELL, A. J. H. (1925) .. The Epidemiology of Cholera. *Indian J. Med. Res.*, **13**, 427.
- Idem* (1927) .. *Cholera Bilibaccine and Anti-Cholera Vaccine : A Comparative Field Test*. League of Nations Health Organization, Geneva.
- SCOTT, H. H. (1939) .. *A History of Tropical Medicine*, **2**, 649. Edward Arnold and Co., London.
- SCUDDER, J. (1940) .. *Shock : Blood Studies as a Guide to Therapy*. J. B. Lippincott Co., Philadelphia.
- TAYLOR, J. (1941) .. *Cholera Research in India, 1934-1940, under the Indian Research Fund Association*. The Job Press, Cawnpore.

BACILLARY DYSENTERY

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Definition.—This is a dysenteric affection, that is, a condition characterized by ulceration of the large bowel and the passage of numerous stools containing blood and mucus. It is acute in its early stages; it is caused by bacilli of the groups *Bacterium dysenteriae* Shiga, *Bacterium dysenteriae* Flexner, and certain other allied organisms.

Historical.—Modern, ancient, and even hieroglyphic and traditional histories are rich sources of evidence as to the existence of clinical dysentery at all periods to which they refer. The first bacterium definitely incriminated as the cause of dysentery was the organism isolated by Shiga in 1898 from 34 out of 36 cases of dysentery. He showed that it was a very toxic organism in that, when injected subcutaneously in the form of a killed culture, it caused a very sharp reaction; he also showed

that the infected patients had specific agglutinins in their blood against this organism. Two years later, Kruse isolated a dysentery bacillus in Germany; this was shown subsequently to be identical with Shiga's bacillus. During the same year, Flexner, and Strong and Musgrave isolated dysentery organisms in the Philippines, and a year or so later, Hiss and Russell associated the so-called 'Y' organism from patients with dysentery in the United States; these latter organisms have been shown to belong to a closely inter-related group of bacteria which are now usually known as the 'Flexner group'. Sonne isolated a dysentery organism that had been responsible for an epidemic in Denmark in 1915.

The first serious attempt at classification of the heterogeneous Flexner group was made by Andrewes and Inman (1919). They showed that there were four antigenic components each of which predominated in one of four different Flexner types (V, W, X and Z), and were more-or-less evenly represented in a fifth (Y), which was probably identical with the original Y of Hiss and Russell. This classification is diagrammatically represented in figure 123.

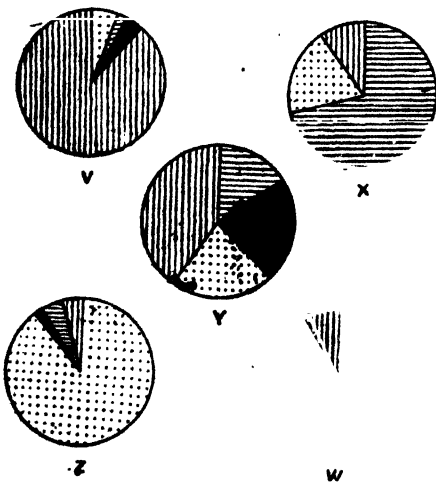


Figure 123: Showing diagrammatically the antigenic structure of the five Andrewes types of *Bact. dysenteriae* Flexner.

Later, Boyd (1940) reclassified this group, added to it and differentiated another group, the representatives of which mainly occur in India: this group he called *Bact. dysenteriae* India, but it is now usually known as *Bact. dysenteriae* Boyd.

EPIDEMIOLOGY

Geographical distribution.—The disease has a world-wide distribution, but is far more common in the tropics and sub-tropics than in the temperate zones; this is to some extent due to backward sanitation in the former areas, though the climatic factor also has some importance.

Without accurate investigation of this particular point, the writer's impression is that Flexner dysentery is the main tropical, Shiga the sub-tropical, and Sonne the temperate-zone type.

Epidemic features.—In temperate climates, bacillary dysentery is an epidemic disease occurring (a) under conditions where for any reason a high sanitary standard is difficult to maintain, or (b) when in special circumstances there is a sanitary breakdown. It is therefore likely to occur in orphanages, mental asylums, concentration camps, and jails on the first count, and is associated with wars, pilgrimages, and migrations on the second. It was at one time known as asylum and jail dysentery, but for many years, in Great Britain at any rate, it has been comparatively rare in these institutions.

In the tropics and sub-tropics it is endemic, but it is still very likely to take on an epidemic form when the circumstances are particularly favourable. In most tropical countries, it is far more common than amœbic dysentery, although until recently the latter was popularly supposed to be the more common.

In temperate climates it is a seasonal disease and almost always associated with the summer or early autumn. In sub-tropical countries, such as Egypt, it is still a hot weather disease, but in very hot countries, such as Iraq, epidemics stop dramatically in the hottest weather when the flies disappear, to reappear for a short time when it cools down again. In the true tropics, its seasonal distribution tends to disappear to some extent, and such undulations in the incidence curve as there are, tend rather to follow the fly curve rather than the thermometer.

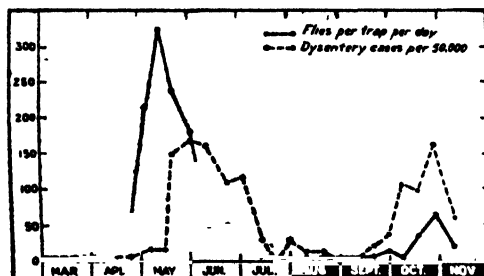


Figure 124 : Showing the rôle of the fly in the spreading of dysentery (Taylor, 1919).

There is no difference in the sex incidence, and people of all ages are liable to suffer from bacillary dysentery. In dysentery epidemics in temperate climates, children figure most prominently; and the disease is also an important cause of infantile and child mortality in the tropics (*cf.* amœbic dysentery which is uncommon in children).

ÆTIOLOGY

The causal organisms : Classification.—The present position of the dysentery organisms is as follows :—

(i) *Bacterium* dysenteriae* Shiga, also called *Bacterium shigæ*; a biochemically and antigenically distinct organism, usually associated with the severest forms of dysentery in tropical countries.

(ii) *Bacterium dysenteriae* Flexner, also called *Bacterium flexneri*; a biochemically similar but not identical group of organisms, of which there

* The generic name *Shigella* is now accepted by bacteriologists, and the word is coming into general use in America, but, as it is at present a little confusing for clinicians, it has been avoided here.

are at least nine antigenic strains recognized. It occurs in tropical and non-tropical countries, and in the former causes at least 50 per cent of the bacillary dysenteries, which may be mild or severe.

(iii) *Bacterium sonnei*, isolated in a small percentage of dysentery cases in the tropics, but more frequently associated with epidemics of infantile and adult diarrhoea in temperate countries.

(iv) Other rarer organisms, e.g. *Bacterium ambiguum* Schmitz, and organisms of doubtful pathogenicity, e.g. *Proteus morgani*, *Bacterium alkalescens*.

Staining, morphology, and biochemical reactions.—The dysentery bacilli are all gram-negative non-motile (with the possible exception of the Newcastle bacillus) rods, 2 to 3 μ by 0.6 μ , that grow readily at an optimum temperature of 37°C., on ordinary laboratory medium, forming clear semi-translucent colonies: they are aerobes and facultative anaerobes. They are all lactose non-fermenters, except *Bacterium sonnei* which is a late lactose fermenter; they reduce nitrates to nitrites, and they give a negative Voges-Proskauer reaction; the differential biochemical characteristics are shown in table V.

Resistance.—Dysentery bacilli are killed at a temperature of 55°C. in one hour, by 0.5 per cent phenol in 6 hours, and by 1 per cent phenol in 15 to 30 minutes. They resist drying for 20 to 25 days. They survive in water and milk for a few days only, but in the latter they will survive for 17 days if the alkalinity is maintained, and in soil they live up to 100 days.

TABLE V

Shows sugar reactions of dysentery bacilli (after Topley and Wilson, 1936).

	Glucose	Mannitol	Lactose	Saccharose	Dulcitol	Rhamnose	Sorbitol	Litmus milk	Indole
<i>Bact. dysenteriae</i> Shiga ..	A	—	—	—	—	—	—	sl A	—
<i>Bact. ambiguum</i> Schmitz	A	—	—	—	—	A	A \mp	sl A	+
Newcastle bacillus ..	A g	A (g)	—	—	A (g)	..	—	sl A sl alk	—
<i>Bact. dysenteriae</i> Flexner	A	A	—	A \mp	—	A \mp	A \pm	sl A sl alk	\pm
<i>Bact. sonnei</i> ..	A	A	(A)	(A)	—	A	A	A (clot)	—
<i>Bact. alkalescens</i>	A	A	—	—	A	A	A	alk	+
<i>Proteus morgani</i>	A	—	—	—	—	N alk	+

A = acid.
alk = alkaline.
g = a little gas.

\pm = sometimes.
 \pm = usually.
sl = slight.
Brackets indicate late formation.

All are non-motile except *Proteus morgani* and possibly the Newcastle bacillus; all reduce nitrates to nitrites, and are Voges-Proskauer negative.

Toxins.—The only dysentery organism that gives rise to a soluble toxin is the Shiga bacillus. Though possibly an endotoxin, this toxin has some of the more important characters of an exotoxin, and when suitably injected it gives rise to a powerful antitoxic serum. Injected into rabbits it causes diarrhoea, collapse, and paralysis. The ground-up bodies of the Flexner group and Sonne bacilli injected into laboratory animals are toxic, but only in much larger doses (about 20 times) than in the case of the Shiga organism. They do not give rise to very efficient antitoxic sera.

Distribution in the body and the recovery of the organism.—The organisms are confined to the intestinal tract, to the mucosa and submucosa, and the intestinal lymphatic glands; occasionally they will be found in the liver and spleen post mortem. They are recoverable from the stools; the frequency with which they are isolated will depend to some extent on the technique of the bacteriologist and the time that elapses between the time that the stool is passed and the medium is inoculated, but mainly on the nature of the stool and the stage of the infection; for example, stools containing blood and mucus will give a positive result in 60 per cent of cases, those containing mucus only in 20 per cent, and simple diarrhoeal stools in 4 per cent, according to one report in which over 3,000 stools were examined. Another report showed that 68 per cent positive cultures were obtained during the first five days of the disease, 17 during the second five, and only 6 per cent during the third five days. With the new media now in use, much higher percentages should be obtained. The organisms are never isolated from the blood or urine.

Carriers.—It is not uncommon for a patient to continue to pass dysentery bacilli for a considerable time after the acute symptoms have subsided. In one large-scale investigation during the 1914–18 war, it was shown that 7.59 per cent of patients became carriers, and that 2.78 per cent were 'persistent' carriers, that is, they continued to pass bacilli for three months or more. Shiga carriers are less common than Flexner carriers, but the carrier state persists longer in the former, and they pass the bacilli regularly, whereas the Flexner carrier is more intermittent, passing bacilli for two or three days, then, after a clear interval of a month, again passing bacilli for a few more days. Sonne carriers are usually very transient.

New media (*vide infra*) for the isolation of dysentery bacilli have thrown new light on the carrier problem, particularly with regard to the symptomless (or contact) carrier. In some institutions in the United States, it has been shown that ratio of the clinical cases to the symptomless carriers is on the average 1 to 3 or 4, and in one institution it was 1 to 7 in the case of Flexner infections and 1 to 24 in the case of Sonne infections.

Source and dissemination of infection.—Man is the sole source of infection; the infection is spread by cases and carriers. The organisms are excreted only in the stools, and transferred by (a) direct contact—in the case of children, mental patients, and other persons with insanitary habits, (b) through the contamination of food or drink, by patients or more usually carrier food-handlers, and (c) by flies, in conjunction with bad sanitation.

Epidemics, other than those in institutions, in sanitarily advanced European countries are usually traced to a carrier employed in the preparation of food, but in the tropics, while flies are probably the commonest agents of infection, a number of epidemics have been traced to unsatisfactory water supplies.

Routes of invasion.—Invasion is always by the oral route. As in cholera, low gastric acidity probably helps to allow the bacilli to pass through the stomach and invade the bowel.

IMMUNOLOGY

Antigenic structure.—The antigenic structure of the dysentery bacilli is an interesting study; that of the Shiga bacillus is homogeneous, and, though there is some cross-agglutination between it and the Schmitz bacillus, there is no cross-absorption. The Sonne bacillus is also homogeneous and distinct, but the antigenic structure of the Flexner group is heterogeneous; there are at least four distinct antigenic components, which are capable of making a considerable number of combinations. There are however six main antigenic types now recognized, three of the original five Andrewes types, V, W, and Z, and Boyd's 103, P119, and 88, the last probably being identical with the 'Newcastle' bacillus which shows rather different biochemical reactions from the other members of the Flexner group (the X type of Andrewes seems to have disappeared). The polyvalent Flexner agglutinating sera are issued by the Standards Laboratory, Oxford; no. I will agglutinate types V, W, and Z, and is practically identical with the agglutinating serum prepared from the original Y strain of Hiss and Russell, and no. II agglutinates the other three strains. Monovalent agglutinating sera are also available for each separate strain.

Boyd* has also shown that there are, in India at least, other pathogenic types, and monovalent sera have been prepared for three types now designated *Bact. dysenteriae* Boyd, 170 P288, and D1.

Agglutinins.—These appear in the blood between the 6th and 12th days of the disease, but the titre declines rapidly after convalescence, and has often returned to normal levels at the end of three months. In a normal individual, the Shiga titre may be as high as 1 in 20, and in an infected patient it seldom rises above 1 in 500. The Flexner agglutinins may be as high as 1 in 150 in a normal individual, but they usually rise higher than this in a patient. In a patient with Shiga dysentery, the Flexner agglutinins may reach 1 in 800, but the reverse is not true. In Sonne dysentery, the specific titre may reach 1 in 1,000, but often fails to rise above 1 in 100, and the normal person may show an agglutination of 1 in 50.

Immunity.—There is little evidence of the existence of any natural immunity in man. The accurate information on acquired immunity is very sparse, but there is clinical evidence that a considerable degree of immunity to local strains is acquired by a succession of mild infections during residence in a locality.

Little success has attended attempts to produce active immunity by inoculation, and, though vaccines are used in treatment, especially of chronic Flexner dysentery—the Shiga organism being too toxic—any good results that have followed are probably due to the non-specific action of the vaccines. Passive immunity that lasts a few months can be produced by means of anti-serum in the case of Shiga dysentery, but it is not a practical measure. The antitoxic value of this anti-serum is however very well established (*vide infra*).

* In a recent paper Boyd (1940) has attempted to simplify the classification of the large (and enlarging) Flexner (mannitol-fermenting) group. His proposal which is receiving general acceptance, at least in the British army, is as follows:—

Name		Old name	
<i>B. dysenteriae</i> Flexner	I	Andrewes and Inman	V
"	II	"	W
"	III	"	Z
"	IV	Type 103	
"	V	P119	
"	VI	88-Newcastle-Manchester group.	
<i>B. dysenteriae</i> Boyd	I	Type 170	
"	II	P288	
"	III	D1	

PATHOLOGY

Morbid anatomy.—Except that in the acute toxæmic cases there is marked congestion of the solid organs, especially the liver, kidneys and suprarenals in which there may be some toxic necrosis of the parenchyma cells, the lesions are confined entirely to the large bowel, the ileo-cæcal valve, and the last few feet of the small intestine; beyond congestion there is usually little evidence of the disease on the peritoneal surface of the intestine, except possibly in the chronic ulcerative stage where there may be some signs of cicatricial contraction.

The post-mortem picture that is encountered will depend on the severity of the infection and the stage at which death occurs. In the case of Shiga or severe Flexner infection, the following pictures may be encountered : (i) In a very severe case where the toxæmia was intense and death occurred early, the whole or a greater part of the large intestine and lower end of the ileum is lined with a white, or yellow (bile-tinged), fibrinous membrane, suggestive of a diphtheritic membrane. (ii) When death occurs at a slightly later stage in an acute attack, the mucous membrane is intensely red, and is covered by strips of dark greenish-grey, necrosed mucous membrane, that are separating, particularly along the tops of the ridges of the mucous membrane. It is possible, if great care is exercised, to see the condition at this stage *in vivo* by means of the sigmoidoscope. (iii) At a later stage still, the whole mucous membrane is still red, congested and œdematous, and covered with a mucous exudate; in it are a number of greyish areas of deeply necrosed mucous membrane which may have separated and left an ulcer. These ulcers are relatively shallow, but may appear deeper on account of the congestion and œdema of the surrounding mucous membrane. The ulcers are usually but not always transverse; they are irregularly shaped, and they are often confluent, or perhaps only separated by a thin strip of mucous membrane from other adjoining ulcers. The condition at this stage can be seen by means of the sigmoidoscope, but the bowel is very sensitive. (iv) The next stage is that in which all the sloughs have separated, and there are numerous shallow ulcers scattered throughout the large bowel; the rest of the mucous membrane is still unhealthy looking, but it shows a tendency to heal. The condition is well seen by means of the sigmoidoscope. (v) The last phase may be (a) the stage of healing, seen through the sigmoidoscope, or post mortem in patients who have died from other causes. In this stage there will be shallow healing or healed ulcers with little or no signs of cicatricial contraction; the rest of the mucous membrane is now healthy, but may show polypoid thickenings in places, which mark the position of retention cysts; or (b) a stage of chronic ulceration in which secondary infection is playing the major part, and the ulcers have lost their specific character; the condition has now merged into that of chronic ulcerative colitis. It is at this stage that sigmoidoscopic examination is most useful.

In mild Flexner or in Sonne or Schmitz infections, the mucous membrane will be red and inflamed, and in places there may be small abrasions of the surface, or even shallow ulcers. Only very rarely or by accident will such cases come to the post-mortem table, but this condition can be seen with the sigmoidoscope.

Sites of the lesions.—In severe attacks, the whole extent of the large bowel and the last few feet of ileum are involved; however, the main sites of involvement are the sigmoid and rectum, in contrast to amœbic infections in which the cæcum is the most common primary focus of infection.

Histopathology.—In the milder cases, there is a catarrhal inflammation and thickening of the mucous membrane, with œdema, polymorphonuclear infiltration, minute hæmorrhages, and a considerable amount of

mucus and sometimes a little fibrinous exudation. In the severer forms, there is an extension of the inflammatory processes to the submucosa, where the lymph follicles are the most important centres of inflammatory activity. There is in these cases considerable thickening of both the mucous and submucous layers; the inflammatory œdema leads to thrombosis of the veins, with numerous hæmorrhages in the submucosa, and coagulation necrosis causes the death and separation of the mucous membrane. There is sometimes a certain amount of round-celled infiltration of the superficial muscular layers, but the deeper layers and the serous coat are practically never involved. With the loss of the mucous membrane, there is formation of granulation tissue at the base of the ulcer, and new blood vessels develop in the submucous layer; in the healing process, columnar epithelial cells grow in from the edges to cover the base of the ulcer. During the inflammatory processes, even if the mucosa is not destroyed altogether, there is a considerable interference with its architecture, and in the healing process, fibrous changes cause blocking of the mouths of the crypts of Lieberkühn with the formation of mucous retention cysts. Active dysentery bacilli often remain behind in these cysts, which eventually burst through the mucous surface into the lumen of the gut; these cysts are responsible for the intermittent carrier state that occurs in this disease.

The stools.—The typical bacillary dysentery stool is very characteristic, both macroscopically and microscopically. In the first few stools, the normal bowel content will be emptied; after this the patient passes very little faecal matter, but a whitish gelatinous mucus flecked with blood, and later, bright-red gelatinous mucus, which has exactly the appearance of red-currant jelly, is very viscid, and adheres to the bed-pan, in a background of brown watery fluid. The stool has an albuminous smell and an alkaline reaction.

Microscopically, it is a very cellular picture, with very few bacilli and little debris to be seen; the cells are (a) polymorphonuclears showing little degenerative change, (b) red cells lying singly or in small rouleau formations, but never clumped, (c) columnar epithelial cells, and (d) large macrophages that simulate amœbæ as they often contain red cells and may even show slight amœboid movement.

Blood picture.—There is nearly always a slight but distinct leucocytosis, which does not however usually rise above 15,000 per c.mm.; there is a relative increase in polymorphonuclears. This leucocytosis is absent in the later stages, and there may even be a slight leucopenia. In the acute choleraic attacks of Shiga dysentery, there will be some polycythæmia on account of the fluid loss and consequent concentration of the blood, and in the later stages, there is often a distinct anæmia, probably of toxic origin. In chronic dysentery there is very frequently a macrocytic anæmia of nutritional origin.

SYMPTOMATOLOGY

The clinical attacks caused by the specific dysentery organisms vary from a mild diarrhœa, in which the patient is scarcely inconvenienced at all, to a very severe toxæmic attack which simulates a severe attack of cholera; in neither of these extreme cases does the true dysentery picture appear. The fully developed syndrome also shows a wide range of variations, from the case in which blood and mucus are passed for a few days only, with little or no constitutional disturbances, to the severe case in which the patient passes countless stools of pure blood and mucus for several days, at first with a severe febrile reaction and later with exhaustion and collapse.

There is no absolute correlation between the type of infecting organism and the clinical attack. Though the pathological potentialities of the various organisms have been indicated above, it is perhaps worth repeating here that the severe toxæmic forms are nearly always caused by the Shiga organism, the milder forms by the Sonne, Newcastle, and Schmitz organisms, whereas the Flexner group may cause anything from a mild diarrhoea to a severe dysenteric attack.

The division into different clinical types is really artificial, as there is an infinite variety of types of all degrees of severity, and it seems more important that the physician should appreciate this fact than that he should learn to apply certain names to arbitrarily selected types, *e.g.* the latent, the mild, the acute, the fulminant, the choleraic, the typhoid, the relapsing, and the chronic; though all these types are clearly recognizable, there are many intermediate types that will defy accurate classification.

The clinical picture, in what might be called the **acute type** of Flexner or Shiga dysentery, is described.

The **incubation period** may be as short as 24 hours, but it is usually found to be between three and seven days; it is seldom longer, in contrast to the incubation period in amœbic infection which is often very long.

The **onset** is usually sudden, with fever and severe diffuse griping pains in the abdomen; this is soon followed by the passage of a loose stool which does not relieve the pains. The interval between stools rapidly decreases, the pain in the abdomen continues but becomes more localized to the left lower quadrant, and the passage of the stools is accompanied by tenesmus. The nature of the stools also undergoes a rapid change; the lower bowel having been emptied of all fæcal matter, the stools consist of a brown watery fluid in which there is much blood-flecked mucus. Meanwhile, the general constitutional condition of the patient rapidly deteriorates; the **fever**, which in some cases precedes the onset, may rise to 103°F. or higher, but the temperature chart is usually a very irregular one at a slightly lower level. Symptoms develop, and eventually the patient is passing nothing but blood and mucus, and is more or less continuously on the bed-pan; it may, in fact, be worth arranging this in such a way that the patient does not have to be repeatedly disturbed and can pass his stools as he lies. The most distressing symptom is usually the tenesmus, which may be almost continuous and helps to exhaust the patient as much as any other symptom; there will often be vesical tenesmus or even strangury which is also very distressing.

The fever will usually continue throughout the attack, and, provided the patient is not collapsed, it is a good guide to progress. The pulse is usually disproportionately rapid, the tongue is coated, the abdomen is flat, and may be rigid and tender suggesting appendicitis, but the tenderness soon becomes localized to the left side of the abdomen, and the thickened and contracted descending colon can often be felt if the patient has a fairly thin abdominal wall.

Progress.—If no treatment is given, toxæmia and exhaustion develop, and the patient may die, or the condition may pass into the typhoid state with fever and continuous dysenteric stools which, even if the patient recovers eventually, will lead to a chronic dysenteric condition with permanent damage to the mucous membrane of the large intestine that will affect the patient's health for the rest of his life. In the moderately severe attacks in which ordinary treatment is given, the disease runs a course of 7 to 14 days before all the acute symptoms subside, but naturally much will depend on the virulence of the organism, the resistance of the patient, and the treatment given.

In severe Shiga infections, the onset may be with a mild diarrhoea and very little fever; the condition becomes rapidly worse, with the development of fever and the passage of innumerable stools consisting of pure blood and mucus; exhaustion follows rapidly, and early death occurs. On the other hand, the symptoms may be mainly due to the toxic action of this organism: cyanosis and later extreme pallor, a fall of blood pressure, abatement or disappearance of abdominal pain and tenesmus, the passage of profuse watery stools, and vomiting, or sometimes abdominal distension and/or acute dilatation of the stomach, conditions suggesting cholera of the classical or of the *sicca* varieties.

Clinical types.—The term *latent* is sometimes applied to the sub-clinical infection, and *mild* may mean nothing more than an acute diarrhoea or the passage of blood and mucus for a day or so, without constitutional symptoms, but in either of these cases the patient may continue to pass dysentery bacilli for some time—and thus be a source of infection to others—and at some subsequent date a relapse, which may be much more severe than the original attack, may be precipitated by some secondary factor, such as exposure to cold, or a dietetic indiscretion.

The word *fulminant* is usually applied to the very acute attack with passage of pure blood and mucus, exhaustion, toxæmia, and death in a few days, and for the *choleraic* type, no further description is needed than the statement that the attack simulates cholera (*q.v.*). In the *typhoid* type, after the acute dysenteric symptoms have subsided, the general condition of the patient does not improve, the temperature continues, and a toxæmic state develops.

Recurring, or relapsing bacillary dysentery.—It is very often the experience of new arrivals in a tropical country that they suffer a succession of mild attacks of dysentery, which keep them in a continual state of sub-health, for a period of a year or more. If none of these attacks has been very severe, such persons will eventually settle down and possibly suffer no further from bowel disorders as long as they remain in the country.

These attacks should be classed as *recurring* rather than *relapsing* dysentery, as they are almost certainly examples of reinfection with different strains of dysentery bacilli, which continue until the individual has acquired a specific immunity to all the common local strains, or a group immunity that is sufficiently well developed to afford protection against all allied dysenteric strains. If a careful bacteriological examination is carried out, it will usually be possible to isolate a Flexner-group bacillus, or more rarely an organism of one of the other species, on each occasion.

Those who are less fortunate will include in their early experiences one or more attacks of a much more severe kind, which will leave their bowel mucosa considerably damaged, so that it is never quite one-hundred-per-cent functionally efficient, and possibly with a number of healed ulcers, the bases of which are covered with a thin layer of mucous membrane over scar tissue, that is very liable to break down under any adverse dietetic circumstances. Such individuals will often never have a really formed stool; after breakfast they pass one or two loose stools, but for the rest of the day they may have no further trouble. In these cases, the main dysfunction appears to be failure of absorption in the lower bowel. Periodically, as the result of a chill, a dietetic indiscretion, or some other cause, they will have a relatively mild relapse of their dysenteric condition, with the passage of mucus but probably not blood, abdominal discomfort, and perhaps mild constitutional symptoms. It is sometimes said that on these occasions dysentery organisms will be recovered from the stools, but this is certainly not the rule, and probably it is from the stools of those

patients who are incidentally carriers that the dysentery organisms are recovered; the association of the carrier state with this condition is really accidental, though both conditions have a common cause. These cases are usually classed as relapsing bacillary dysentery but they are really mild forms of chronic ulcerative colitis.

Chronic (bacillary) dysentery.—The distinction between this group and the previous one is really only a matter of degree. The word bacillary is retained only to indicate the ætiology and to distinguish it from the other chronic sub-acute ulcerative condition in which there is an amœbic infection still present (*vide infra*). In these chronic ulcerative conditions of the colon, there is no specific bacillary infection left, and the condition is best considered under the heading **chronic ulcerative colitis**.

Complication and sequelæ.—There are few true complications in bacillary dysentery, in contradistinction to amœbic in which there are many. One of the commonest and most troublesome is **arthritis**. It is very similar to the condition produced by gonorrhœa; the joints affected are the knees, ankles, wrists, elbows, fingers, occasionally the sterno-clavicular and temporo-maxillary, and rarely other joints. One characteristic is the fleeting nature of the arthritis, and its habit of flitting from joint to joint. The frequency of its occurrence varies in different localities, and from epidemic to epidemic in one locality. In some places it is rare, and in others it may occur in 10 per cent of patients. The pain is out of proportion to the redness and swelling, which may be very slight. On the other hand, **hydrarthrosis**, especially of the knee joints, is not uncommon. The fluid is usually sterile but contains the specific dysentery agglutinins, often in relatively high titre.

Arthritis usually appears within the first few weeks of the attack, but on some occasions the onset is postponed for as long as three months. The condition may persist for a month or so, but quite frequently it clears up in a few days. Seldom, if ever, does it produce any changes in the joints or lead to chronic arthritis, though the fact that it is apparently more common in rheumatic subjects might mislead one into arriving at this conclusion. It is more common following Shiga, but does occur after Flexner infections.

Eye complications are not uncommon, conjunctivitis coming on during the acute attack, or later, during the third to the fifth week, and iridocyclitis, or anterior uveitis coming on during convalescence. There is marked tenderness, photophobia, and blepharospasm.

Acute parotitis is not uncommon, and in some epidemics an acute suppurative parotitis has been described.

Intussusception is not uncommon in children, and a lookout for a sudden increase of abdominal pain with obstruction should be kept.

Neuritis occurs sufficiently frequently after bacillary dysentery to associate the two conditions; the legs are mainly affected, there being loss of knee jerks, hyperæsthesia of the calves, muscular spasms and cramps, paralysis, and atrophic changes in the skin, the condition persisting for a month or so.

Achlorhydria has been observed in a large number of convalescents from bacillary dysentery, and the question has arisen, here again, whether this is the result of the infection or whether it is evidence of the special susceptibility of those persons with naturally low gastric acidity.

Nutritional disorders.—Megaw was of the opinion that **post-dysenteric ascites** was not uncommon, and suggested that this was due to a toxic peritonitis. The observation is probably correct, but the interpretation seems questionable. There are probably a large number of nutritional disorders that follow the extensive damage which the mucous membrane of the bowel suffers; these are not yet fully understood, and the ascites may well

be an indirect sequel due to liver damage. Napier and Neal Edwards (1941) considered that there was an association between macrocytic anæmia in pregnancy and bowel disorders, and the writer (Napier, 1939) has frequently associated nutritional macrocytic anæmia with diarrhoea and dysentery.

Terminal.—The patient with relapsing dysentery who does not receive appropriate treatment, or who fails to respond to treatment, will usually die of exhaustion and asthenia, but pneumonia as a terminal event is not uncommon in cold climates.

DIAGNOSIS

In the typical attack, the clinical diagnosis of dysentery does not present any difficulty, but it is very important, especially from the point of view of treatment, to distinguish between the amœbic and the bacillary infections, and in the latter case to decide whether the infecting organism is *Bacterium shigæ* or one of the other dysentery organisms. Some of the differences between the typical Shiga and typical Flexner dysenteries have been indicated above, but, wherever possible, bacteriological investigation should always be undertaken. A table of the main differences between amœbic and bacillary dysentery is given at the end of this section.

The milder forms of bacillary dysentery may be difficult to distinguish from ordinary digestive upsets, and the fulminant choleraic type from true cholera. In view of the possibilities of more serious development, an accurate diagnosis in the milder types is important to the patient himself; and, from a public health point of view, as a signal to tighten up all sanitary precautions, it is even more important that the true nature of such an infection should be revealed. In the choleraic attack of dysentery, the immediate treatment is practically the same as for true cholera (intravenous saline therapy), and anti-dysenteric serum given to a cholera patient will do him more good than harm, though there are obviously more economical ways of giving him an effective treatment; but here again the public health point of view demands a bacteriological diagnosis, on account of the far greater powers of rapid dissemination of the cholera vibrio.

Stool examination.—**Macroscopic inspection** (*vide supra*) will give very valuable information. In Mesopotamia during the 1914–18 war, the writer knew a competent pathologist who claimed that he could make as accurate a diagnosis by inspection and a piece of litmus paper as with a microscope; however, he only adopted the procedure during the worst rush periods.

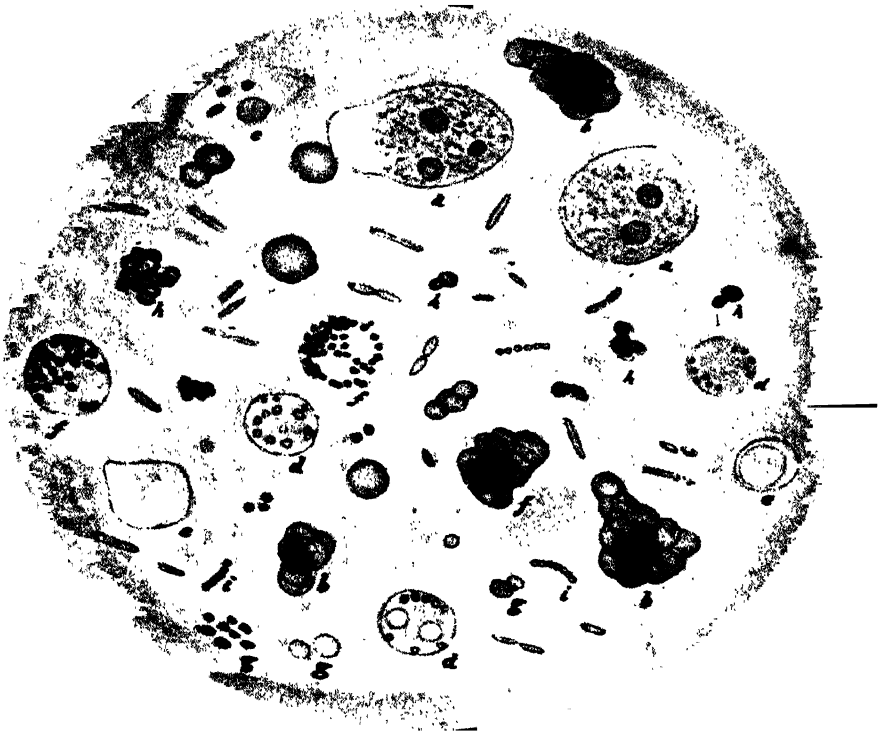
Microscopic examination.—With a platinum loop, or any piece of wire or a match stick, a small portion of stool, preferably a piece of mucus if any is visible, should be picked up and placed in a watch-glass, normal saline added, the stool broken up or the mucus teased out, and the two well mixed; a loopful is then transferred to a slide and a coverslip placed over it. If the edges of the coverslip are vaselined, the examination will be carried out more comfortably; in a dry climate this precaution is essential.

Strong presumptive evidence that the attack is bacillary in origin will usually be obtained from the typical picture presented and the absence of amœbæ (*see* table VI, p. 413, and plate XII).

Bacteriological examination.—The two most important points for the clinician to remember are that the earlier the stool is sent, the better are the chances of isolating the causal organism, and that the specimen must reach the pathologist with the least possible delay after the stool is passed.

The sequence is so often as follows:—In the case of a sub-acute attack the physician is not called in for the first few days; he then calls at the patient's house and makes a provisional diagnosis of dysentery, but the patient has not

Typical microscopical appearance of the stools



In amebic dysentery.



kept his stool; the next day the patient passes a stool at 6 a.m., the doctor calls at 11 o'clock, takes a specimen which he carries round in his car until 2 o'clock and then sends to the pathologist, so that with luck the stool is plated at 3 o'clock. In such circumstances, it is not surprising that a positive diagnosis is so seldom made in private practice; the wise practitioner will send his patient to the pathologist, if he is fit enough, and, if not, arrange for him to send a specimen direct, immediately it is passed, or he will obtain the suitable medium from the pathologist, plate the stool himself, and send it to the pathologist for the identification of the organisms.

In sending the specimen to the pathologist, a portion of stool containing mucus should be selected. To plate a stool, the specimen should be poured out into a sterile petri-dish and, if it is formed or semi-formed, a little saline added. After careful inspection, a piece of mucus is selected; this is picked up on a platinum loop and transferred to a watch-glass containing sterile saline in which it is washed; the platinum loop is flamed; the mucus is again picked up, and drawn a number of times across the surface of 'plate', or on a series of test-tube slants, of some suitable solid medium. If there is no mucus, a loopful of fluid stool should be 'stroked' across the plate or tubes.*

* There are several new 'selective' media on which the growth of the ordinary saprophytic organisms in the stools is inhibited, so that the pathogenic organisms grow and are easily identified. A good example of such a medium is SS (Shigella-Salmonella) agar, the composition of which is as follows:—

'Bacto' beef extract	5.0 grammes
Proteose-peptone	5.0 "
'Bacto' lactose	10.0 "
'Bacto' bile salts no. 3	8.5 "
Sodium citrate	8.5 "
" thiosulphate	8.5 "
Ferric citrate	1.0 gramme
'Bacto' agar	17.0 grammes
'Bacto' neutral red	0.025 gramme

To prepare the medium for use, suspend 63.5 grammes in 1,000 c.cm. of cold distilled water. Boil for a minute or two to dissolve the medium completely. Do not sterilize in the autoclave. About 20 c.cm. of the medium should be poured into standard petri-dishes of 90-100 mm. diameter. It is very important that the surface of the plates be quite dry when inoculated, and this may be ensured by allowing the medium to solidify and to stand for about 2 hours with the covers of the plates partially removed. The final reaction of 'Bacto' SS agar is pH 7.0. The main constituents are Difco 'Bacto' products which are not always available, in India at least; for this reason Panja and Ghosh (1943) have modified the original SS medium, and prepared a medium, which also unfortunately has many foreign ingredients. In the writer's personal experience very good results have been obtained with this medium in enteric, dysentery and cholera cases.

The constituents are:—

Lemco (Oxo, Ltd.)	0.50 per cent.
Peptone (Difco)	0.50 " "
Sodium taurocholate	0.85 " "
" citrate (Merck)	0.80 " "
" thiosulphate (Merck)	0.85 " "
" phosphate (Merck)	0.75 " "
Ferric citrate	0.30 " "
Lactose (Merck)	0.25 " "
Agar	2.50 " "
Neutral red, 0.25 per cent (Grübler and Co.)	1.5 c.cm. to 100 c.cm.

Stock agar prepared from Lemco, peptone, bile salts, and agar, 7.0 pH, is kept ready in 100 c.cm. quantities. This is melted, and to it sodium citrate, sodium thiosulphate, ferric citrate, and neutral red in the requisite quantities are added.

Sodium hydroxide (2 N), 0.5 c.cm., is then added to make the final pH 7.4; the medium is then boiled for two minutes, and poured into plates.

These media should be inoculated heavily with a generous sample of stool.

As has been indicated above, the percentage of positive findings will vary considerably in different circumstances, and will depend on the nature of the stools and the stage of the disease (*see p. 403*).

Serum agglutination.—Though suggestive agglutinations will often be obtained (*vide supra*), this method is of little practical value in the diagnosis of bacillary dysentery, on account of the late development and the relatively low titre of the agglutinins; even as a measure of retrospective diagnosis, its value is limited on account of the early decline of the agglutinins.

As a general rule it may be said that at 1 in 40 standard agglutination of *Bacterium shigæ* is very suggestive, and a 1 in 100 agglutination of *Bacterium flexneri* in the absence of any agglutination with *Bact. shigæ* (an agglutination of *flexneri* as high as 1 in 800 has been reported in a pure Shiga infection) is also suggestive, but a rising titre is a more reliable indication in either. Nothing less than 1 in 100 should be considered as indicating a Sonne infection, and, as the titre often fails to rise above this, not much help will be obtained in this infection.

Sigmoidoscopy.—This procedure plays no part in the routine diagnosis of the fulminant forms of dysentery, though some invaluable confirmatory information regarding the pathological changes that take place in the mucous membrane during such attacks has been obtained by this procedure. The condition of the bowel must be deduced from other evidence, as sigmoidoscopy is not only extremely painful, but may be dangerous in the very acute stages of the disease. In the ordinary acute, in the sub-acute, and in the chronic types, it may be very valuable as a diagnostic procedure, a guide to treatment, and an indicator of progress under treatment. The general state of the mucous membrane can be seen, the extent and the stage of ulceration and/or the degree of healing of the ulcers ascertained, and the nature of the ulcers identified, by their macroscopic appearance and also by taking swab specimens directly from the ulcerated surface and examining them.

In an acute or sub-acute dysentery in which blood and mucus is being passed, if there is no general inflammation of the mucous membrane, bacillary dysentery can usually be excluded, and a diagnosis of amœbic dysentery made.

Technique.—In the preparation of the patient for sigmoidoscopy, it is inadvisable to prescribe a purgative, but a light non-residue diet should be given on the previous night, and a soap and water enema in the morning; this should be followed by an alkaline saline washout. It is essential that the enema and washout should not be retained, and the patient must be encouraged to pass them, by gentle exercise if possible. Nervous or sensitive patients should be given $\frac{1}{2}$ of a grain of morphia half an hour before the examination. The best position for the examination is a modified lithotomy position with the legs suspended by the knees, and the buttocks raised. An alternative position, more suitable for the bed, is with the patient lying on the right side with the legs drawn up, but again if possible the buttocks should be raised so that any fluid left in the bowel will tend to flow away from the sigmoidoscope.

The sigmoidoscope is very cautiously inserted for about 3 inches in the direction of the umbilicus, the bougie is then removed, the lamp inserted, and all subsequent advances of the instrument are made under visual guidance, with the aid of the inflation apparatus. As each portion of mucous membrane comes into the field, it is examined; it may be necessary from time to time to remove mucus by gentle swabbing. The instrument must only be advanced when the operator can see a clear passage, which will often have to be created by gentle inflation. By means of sterile swabs, specimens can be taken directly from the ulcers for culture and/or microscopical examination.

PREVENTION

The application of the general principles of sanitation, especially with reference to water supply, food, faeces disposal, and flies, is the only real

TABLE VI
Contrasting bacillary and amœbic dysentery

	<i>Bacillary dysentery</i>	<i>Amœbic dysentery</i>
EPIDEMIOLOGY ..	Epidemic in temperate climates; endemic and epidemic in tropics. Common in children	Endemic and rarely epidemic; mainly tropical.
PATHOLOGY		Less frequent in children.
<i>Bowel</i> ..	Depressed serpiginous ulcers often transverse, in thickened and inflamed mucous membrane. Sigmoid and rectum mainly, also lower end ileum.	Deep oval or round ulcers with raised undermined edges in healthy mucous membrane; all layers affected; cæcum and flexures, never ileum.
<i>Stools</i> ..	Very frequent, scanty, viscid mucus, non-offensive, bright red blood or red-currant jelly. Alkaline Very cellular, polymorphs (not degenerated), columnar epithelial cells and macrophages; RBCs discrete.	Less frequent fæcal, bulky, offensive, dark blood and mucus or anchovy sauce. Acid. Not very cellular, degenerated lymphocytes; clumped RBCs; Charcot-Leyden crystals, active amœbæ containing red cells.
<i>Blood</i> ..	Leucocytosis only in acute stages, subsequently normal or leucopenia.	Usually leucocytosis, increases with liver abscess.
SYMPTOMATOLOGY		
<i>Incubation</i>	A week or less	A fortnight to many months.
<i>Onset</i>	Acute	More often insidious.
<i>Fever</i>	Usual	Rare.
<i>Abdominal pain and tenderness.</i>	Severe, localizing to left side	Variable, may be severe, localizing to right side.
<i>Tenesmus</i> ..	Usually severe	Less severe, often absent.
<i>Terminal</i> ..	Toxæmia and exhaustion	Exhaustion and complications.
<i>Complications and sequelæ.</i>	Few; polyarthritides	Peritonitis and hæmorrhage; hepatitis and liver abscess common. Multifarious sequelæ.
SIGMOIDOSCOPY ..	Not good practice in acute stages; red inflamed mucous membrane, readily bleeds, rigid bowel wall, ulcers seldom seen.	Permissible in sub-acute attack; raised button-like ulcers or numerous minute ulcers (mouse-eaten appearance) with red edges, in normal mucous membrane.
THERAPEUTIC TEST ..	No response to emetine	Marked improvement with three 1-grain doses emetine on three successive days.

preventive measure. A marked fall in the incidence of dysentery in a community, such as a tea-garden labour force, follows the introduction of a protected water supply; a further reduction, almost to the point of elimination, will be achieved by the establishment of a satisfactory latrine system, when this is possible. In institutions and other communities which have common feeding arrangements, a careful search for carriers should be made amongst food-handlers, and dysentery convalescents should not be employed in this capacity, at least for many months and after repeated bacteriological examinations.

There is no evidence that prophylactic inoculation is of any value.

RURAL SANITATION

Rural water supplies and water disinfection have been discussed above (p. 386); a reference to rural sanitation would perhaps be appropriate here.

Rural sanitation, particularly in India, is not a problem that is likely to be solved by any single formula; the conditions are far too varied. However, the

one recent advance in sanitary engineering that has come nearest to providing this solution is the bored-hole latrine. Notes on this subject, kindly given to me by Mr. B. R. Dyer, professor of sanitary engineering at the All-India Institute of Hygiene, Calcutta, have been amplified from a paper by Mr. G. Ghosh (1942) of the same institution, and are given below :—

Bored-hole latrine.—The bored-hole latrine appears to be the best solution for disposal of rural sewage; but, unfortunately, in the past, there has been, on the one hand, over-enthusiasm on the part of the supporters of the bored-hole latrine, and, on the other, the expression of adverse opinions by people little acquainted with soil hydraulics and the mechanism of the contamination of sub-soil water. It is always desirable wherever possible that bored-hole latrines should be bored below the water table in order that the latrine may act in somewhat the same manner as the septic tank. In recent extensive experiments, it has been shown that pollution of sub-soil water is dependent upon the texture and alkalinity of the soil, and on the slope of the water table.

In a very coarse sub-soil, it has been found that contamination from a bored-hole latrine may spread, in the direction of the flow of sub-soil water, to an extent of several hundred feet, but, on the other hand, in a fine alluvium soil, as in the Punjab, for example, bacteriological pollution only extended to $7\frac{1}{2}$ feet from the bored-hole latrine in the direction of the flow. In a more acid soil and one of a somewhat coarser texture than that in the Punjab, after $2\frac{1}{2}$ years' observation, pollution only extended to 15 feet from the bored-hole latrine in the direction of the flow.

The advantage of the bored-hole latrine is that it is easy to install and very cheap; having a small diameter, the faeces are incorporated quickly in the soil in the bored hole. There is no smell when the surface of the content of the latrine is more than 3 feet from the ground surface, and there is no breeding of flies. It has been shown—by reborings—that four months after a bored-hole latrine has been abandoned, the faeces are incorporated in the soil. The life of a bored-hole latrine for a family of five is usually about one year; after the hole has been filled to within 3 feet of the surface with soil, and abandoned, the squatting plate and the superstructure can be moved to another site.

Construction.—The bored-hole latrine is a round hole bored into the earth with special auger 16 inches in diameter. The depth to which it is bored depends on the sub-soil water level. There should be a minimum of about 3 feet of water during the dry season.

A hole about 6 inches deep and 16 inches in diameter is first dug, and the auger is placed in this hole and rotated in a clockwise direction. When the auger is filled, it is lifted up and the earth is emptied. It is again put back into the hole, and the process is repeated until the desired depth is reached.

If the soil is very loose and the hole tends to cave in, it can be protected by putting in a bamboo lining (figure 125).

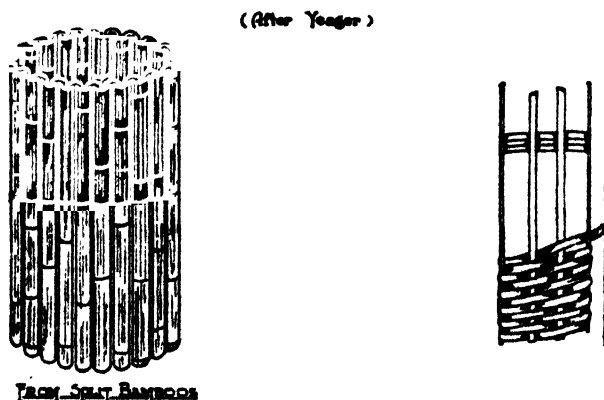


Figure 125

Squatting plate.—This should be of reinforced concrete. Squatting plates 3 feet by 2 feet 6 inches are made of cement concrete in the following proportions : cement 1 part, sand 2 parts, stone or brick chips ($\frac{1}{2}$ inch to $\frac{3}{4}$ inch) 4 parts.

The thickness of the plate throughout is 2 inches. The plate is sloped $1\frac{1}{2}$ inches from edges to centre. The concrete is reinforced with $\frac{1}{2}$ -inch diameter rods (figure 126).

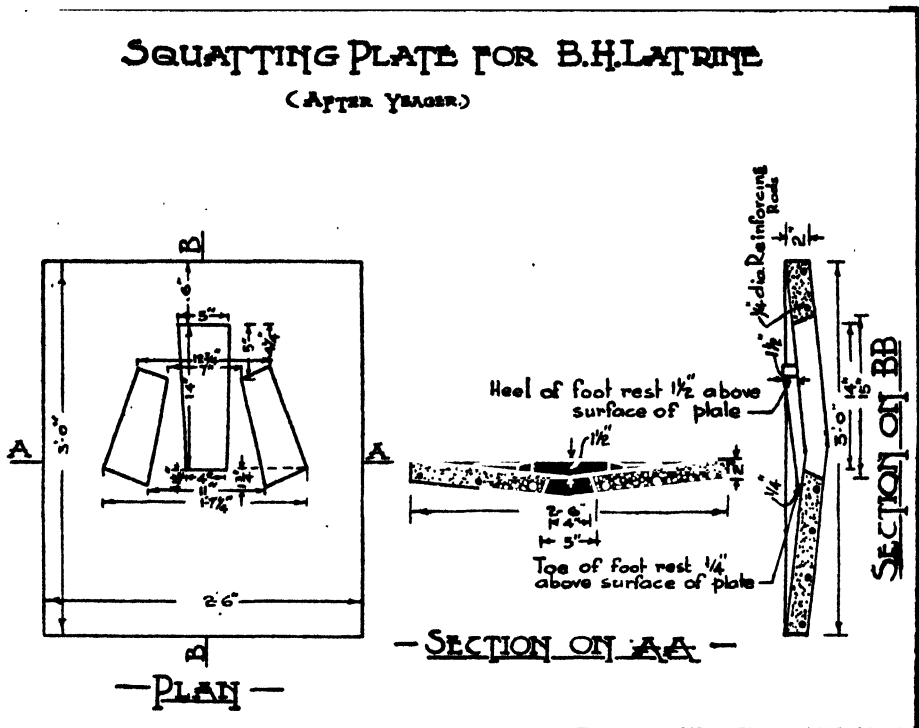


Figure 126

The bare squatting plate with the hole is first cast in a mould. After 24 hours it is removed from the mould, and the top surface is smoothed and the foot rests are added.

It should be noted that the face of the hole in the squatting plate is splayed outwards and downwards so as to have the larger area of the hole on the bottom surface of the plate.

Completed slabs should be kept in a cool place immersed under water for a period of ten days, when they can be removed and fixed over the latrine.

Superstructure.—Any type of superstructure can be constructed. An inexpensive one would consist of side screens of bamboo matting fixed on to bamboo poles.

TREATMENT

Introduction.—Sojourners in the tropics, as well as the indigenous inhabitants, are apt to take a light view of an attack of diarrhoea or mild dysentery, but, since at least 75 per cent of *chronic* ill-health in the sojourner can be attributed to malaria or dysentery—and in some places malaria is unimportant—there is every reason why their medical advisers should take great care not to fall into the same error. In the present state of sanitation in the tropics, mild attacks of dysentery are probably inevitable, but, if the early attacks are treated properly and cured quickly, the patient stands a very good chance of developing an immunity which will protect him against most subsequent infections; if they are not so treated, he will eventually pass through the relapsing and chronic stages to become a permanent semi-invalid with periodically recurring ulcerative colitis. Further, the risk of serious development of the initially mild attack must be fully appreciated.

The specific treatment of bacillary dysentery has always been singularly unsatisfactory. Antitoxic serum, which was introduced about

40 years ago, is of undoubted value, and its dramatic effects in certain cases leave a great impression on the minds of those who see these, but it has never really touched the main problem of the treatment of the millions who suffer from this disease. The main reasons for this are that the serum is expensive to produce, it is difficult to keep and has a relatively short life, it is only really satisfactory in Shiga infections which often form only a small percentage of the cases to be treated and cannot readily be selected from cases of other dysentery infections, and, finally, the vast majority of cases have to be treated under conditions where serum treatment would be difficult or impossible, and/or are of such a relatively mild nature that an expensive, elaborate, and not entirely danger-free treatment does not seem justified.

With the introduction of the many new synthetic drugs, hopes were again raised that some of those might be of value in bacillary dysentery.

Little success was achieved in this direction until recently, though a few observers are of the opinion that some of the amœbicidal drugs, such as yatren and carbarsone (*vide infra*), have a specific action in bacillary infection; this view is not generally accepted. The early sulphonamides gave disappointing results, though in some chronic cases they appeared to help towards the eradication of mixed secondary infections.

Rather surprisingly, sulphapyridine was not used in the treatment of bacillary dysentery for some time after its introduction into therapeutics, and the first reports were not very convincing, probably because an insufficient dose was given, but recently a number of workers (*e.g.* Lapping, 1942) have reported very favourably on it. The drug must be given in maximal doses, and its success probably depends on its reaching the large intestine in sufficient concentration.

The most recent drug of this group is sulphanilyl-guanidine. It is given in much larger doses, and has the special quality that its absorption is low. The results so far reported with this drug, and the writer's own experience, seem to suggest that a really important advance has been made in the treatment of bacillary dysentery. Further, it seems very probable that, in time, other drugs of this group will be produced which will be even more satisfactory.

Procedure.—In a severe dysenteric attack, the main dangers come from toxæmia, ulceration, and exhaustion, and these three processes should always be kept in mind in the treatment of the disease.

Whenever possible the patient should be confined to bed, and in any thing but the mildest attacks, he should not be allowed to leave his bed to defæcate but should be given the bed-pan. In the serious case, this precaution may well make the difference between death and recovery, though of course very frequently circumstances are such that it cannot be observed. At first, practically no food should be given, but a free supply of glucose water or plain water, and, later albumin water, lime whey, and chicken broth may be allowed.

In the mild non-toxæmic case, 60 grains of sodium sulphate should be given in half a glass of water every two hours during the first 24 hours—except when the patient is asleep at night—and every 4 hours subsequently until the main symptoms subside, that is, until the temperature falls to normal, the pain is relieved, and the stools are reduced in number and are more or less free from mucus; then, if by this time the sodium sulphate has been given for at least 72 hours, a drachm of bismuth carbonate, should be given every three hours, or kaolin, a pound in a pint of water, should be placed by the patient's bed and he should be encouraged to sip it frequently.

In the more severe cases, sulphanilyl-guanidine should be given. This must be given in full doses; 0.10 gramme per kilogramme body-weight of

patient for the initial dose, and 0.05 gramme for subsequent doses, every four hours, until the stools are reduced to three or four a day, after which the drug is given every six hours for another two or three days. For an average man of 70 kilogrammes, this will mean 28 grammes during the first 24 hours and 21 grammes during each subsequent 24 hours, until the dosage is reduced to 14 grammes a day; no other treatment is given, except for intravenous glucose saline if this is necessary to combat dehydration.

As alternatives to sulphanilyl-guanidine, if this is not available, sulphapyridine or sulphathiazole is given. The dosage of these must be much lower; two grammes as an initial dose and one gramme three-hourly, in an adult will usually be sufficient.

Even in the most severe cases, this treatment will usually be indicated, but if the patient is very toxæmic, or cyanosed, or if there is evidence that it is a Shiga infection, anti-dysenteric serum should also be given, and/or, if choleraic symptoms develop, intravenous therapy.

Many physicians still adhere to the old-established treatment of an ounce of castor oil with half a drachm of tincture of opium; there is much to be said for this treatment in mild cases, but the writer believes that better results are obtained with sodium sulphate; further, the oil will make subsequent examination of the stools for confirmation of the diagnosis very difficult; and, finally, if there is any doubt about the diagnosis, it must be remembered that opium is definitely contra-indicated in cholera.

Anti-dysenteric serum.—Shiga antitoxic serum, as opposed to the so-called polyvalent serum, should be used, for a number of reasons; the Flexner organism gives rise to a serum of very low antitoxic quality; Flexner infections seldom need antitoxic serum treatment; and, when serum is given, they seem to respond as well to anti-Shiga as to the polyvalent serum.

The antitoxic serum that is usually available to-day is concentrated, and contains about 5,000 antitoxic units to the cubic centimetre. An initial dose of 100,000 units may be looked upon as maximum, and very often 50,000 units will be sufficient; a dose of 50,000 units should be given on the following day; and possibly a third dose, if it appears to be indicated. Whenever possible the antitoxic serum should be given intravenously in half a pint of 5 per cent glucose in normal saline. In a cold climate, the glucose saline should be warmed to body temperature before the serum is added; as severe reactions may follow the administration of overheated serum, the temperature should be tested very carefully. Intramuscular or subcutaneous injections are less satisfactory, as the serum is absorbed slowly and may cause a local reaction. The modern serum is treated with a proteolytic enzyme, so that the danger of anaphylaxis is considerably reduced, if not eliminated, but, in patients who have previously received any form of serum treatment, and if time permits, it may be advisable to precede the intravenous injections by the desensitizing course mentioned below.

There is usually some reaction to the serum treatment, after about 12 hours, in the form of flushing of the face, a slight rise of temperature, and temporary exacerbation of symptoms, but these rapidly pass off and general improvement is soon noted.

If the concentrated serum is not available, it is usually of little use giving less than 60 c.cm. to 80 c.cm. of ordinary antitoxic serum as an initial dose, to be repeated if necessary, and in this case it will always be advisable to precede the main dose by a series of *desensitizing doses* of 0.1, 0.25, and 0.5 c.cm. of serum at 20 minutes' intervals.

The reaction that follows the giving of antitoxic serum must not be confused with, (a) the anaphylactic phenomena that may follow the serum injection if the desensitizing procedure is not adopted; these include cardiac pain, vomiting and

collapse, and they should be countered by injections of adrenaline and pituitrin, or (b) the later serum sickness that may come on six to ten days after the serum is administered, with local pain at the site of the injection, fever, joint pains, and urticaria. A daily dose of calcium lactate will reduce the chances of both these reactions occurring.

Intravenous therapy.—In severe cases, whether of the choleraic type or not, this will often be indicated, and it is useful as a vehicle for the antitoxic serum. Glucose added to physiological saline (25 grammes to 500 c.cm., or about a pint) is the best for the ordinary severe case, but, for the choleraic type of attack, hypertonic saline will probably be more effective. Where there is not very marked dehydration, the drip-feed method will be the best for administering the saline; by this method a pint should be given in about half an hour. When antitoxic serum is not available, normal serum or plasma—a pint added to a pint of glucose saline—may be used with advantage.

Bacteriophage.—There is unanimity of scientific opinion on the fact that, *in vivo*, bacteriophage does not act as it does *in vitro*, and lyse the dysentery bacilli in the tissues. The explanations of its action—if it has any action—that seems most feasible are that it converts pathogenic bacilli into non-pathogenic or less pathogenic organisms, or that the lysate, of those organisms that it does lyse, acts as a vaccine. The writer has never been convinced from his own experience that bacteriophage has any specific action, but it is impossible to ignore the opinion of many experienced practitioners who claim that it is of definite value. Some of these say that it cuts short the attack when given in doses of one ampoule (about 2 c.cm.) every 4 hours; others claim that it is useless in these small doses, and that to obtain any results at all it must be given in large doses, 4 to 6 ampoules every two hours.

To summarize, world scientific opinion is still very sceptical regarding the therapeutic value of bacteriophage in this disease; the writer however recommends that, if it is given, it is given in large doses; even the sceptic's consolation, 'at least it is harmless', is not universally applicable to bacteriophage, but the writer believes that it applies in this case.

Symptomatic.—For the relief of abdominal pain, opium may be given but only in the early pre-exhaustion stage; hot water bags and hot fomentations will help. **Tenesmus**, if it persists, will be relieved by bowel washes, plain water, normal saline, or bicarbonate (60 grains to the pint), followed by six ounces of normal saline to which 20 c.cm. or more normal serum has been added, to be retained as long as possible; as an alternative to this, six ounces of kaolin suspension should be retained.

It may be more convenient to use a suppository; the following will be found useful though, as opium has no direct effect on the mucous membrane, it is not clear how it acts :—

R Extracti opii sicc.	..	gr. ii
" belladonnæ sicc.	..	gr. ½
Cocobutter	..	ad gr. 12

Vesical tenesmus and strangury will be assisted by a belladonna and alkali mixtures :—

R Potassi bicarbonatis	..	gr. xx
Tincturæ belladonnæ	..	℥. xx
" hyoscyami	..	ʒjss
Infusum buchu	..	ad ʒjss
		4 times daily

This will also be relieved by the suppositories and warm rectal washes indicated above. **Soreness of the anus** due to frequent stools can be prevented by careful washing and drying, and by the application of lanoline,

or calamine lotion made with an oily base. **Meteorism** may be an indication of severe toxæmia, but in the later stages of the disease it often indicates an indiscretion in diet. It may be relieved by giving charcoal biscuits or charkaolin, but more active treatment with turpentine stupes, etc. (see p. 475) may be necessary. Vomiting and hiccough may also be troublesome (see p. 396). For **collapse**, the usual treatment for this condition, hot water bottles, etc., should be supplemented by intravenous saline therapy, with if necessary the addition of pituitrin.

Diet.—As was noted above, no food should be given for the first 24 hours, but barley water made with glucose should be allowed *ad lib.*, and then lime whey, albumin water, arrowroot, and chicken broth; it is important also to give some form of fruit, and in India and other countries where this fruit grows, bael fruit made into the form of a 'sherbet' for drinking, or into a 'fool', is perhaps the best. Orange juice or other fruits, as long as they are put through a strainer, may be given. The feeds should be given in small quantities at short intervals, say every two hours. The diet must be extended slowly; there is a strong tradition against the use of milk in dysentery in India, but milk foods are too useful as invalid dietary to be excluded altogether. Skimmed milk should be given at first; it may be citrated, given in the form of buttermilk, prepared with Benger's food, or better still fortified by the addition of casein. Horlick's milk is also a good alternative at a later stage. Bulgaricized milk is sometimes very useful in more chronic forms of bacillary dysentery, to change the intestinal flora. Then, eggs in the form of flip, marmite and toast, jellies, and vegetable purees may be added. The return to a full diet should be slow.

As a general rule, in Flexner infections the diet should be predominantly protein, and in Shiga infections predominantly carbohydrate.

Special diets.—Great success has been claimed for the apple diet. As much as 3 pounds of finely minced apples are given during the day to the exclusion of all other food, for about three days. Dried apple powders have been placed on the market for this purpose. The writer's limited experience with dried apple powder diet was inconclusive.

Bael or bananas have been used as alternatives where these fruits are available.

Treatment of recurring bacillary dysentery.—For each fresh attack the same routine should be applied, but it will seldom be necessary to go to the extent of giving anti-dysenteric or intravenous saline. As the diagnosis of amoebic dysentery will probably have been excluded at the first examination—though it is unsafe to assume without further examination that an amoebic infection has not been super-imposed—it will be possible to give castor oil. The patient should be put on casein-fortified skimmed milk, or buttermilk, or as alternatives, bulgaricized milk, or Benger's food. Castor oil emulsion—a drachm to the ounce—should be given four-hourly for the first day, followed by bismuth carbonate in doses of gr. xx three times a day, until the symptoms subside. Then, to prevent further recurrence, the diet will have to be regulated very carefully for some time (see below), and ispaghula (or one of the proprietary preparations, Isogel, Normacol, etc.), a tablespoonful nightly, and liquid extract of kurchi, a drachm three times a day, taken for a number of weeks. The best form of ispaghula is the ordinary Indian bazar *bhusi*, which is the husk of the seed; this is placed in half a glass of water and after being allowed to soak for a few minutes is swallowed quickly. If it is left too long, the husks swell and the draught becomes a soft gelatinous mass which may be mechanically easier to swallow but is very nauseating to some tastes. Where this is not available, the bowels should be regulated by means of one of the agar-agar and liquid paraffin preparations (e.g. agarol or petrolagar) very carefully

for a time, but the possibility that these absorb and retain vitamins must be remembered. When some other purgative is necessary, senna pods should be used.

The treatment of the truly chronic condition will not be considered here, but it must be remembered that there is no sharp line of distinction between this recurring condition and chronic ulcerative colitis (*vide infra*), and many physicians will recommend the early administration of the medicated enemata that are the mainstay of the treatment for this latter condition.

Vaccines.—These have never found any place in the treatment of the acute attack. Their advocates have claimed useful results in chronic cases in which the original causal organisms are still present. For these they advocate autogenous, or at least homologous, dysentery-group vaccines, as well as 'sensitized' vaccines, prepared by treating the vaccines with homologous serum.

Others have used autogenous vaccines of various other organisms obtained from the patient's stool, on the assumption that they are the organisms causing the secondary infection of the ulcers, sometimes picking out certain special organisms, *e.g.* *Bact. pseudo-carolinus*, which—for no very apparent reason—they particularly suspect. The writer has seen striking results follow the administration of these vaccines in certain cases, which results he attributes to a combination of psychological effect and protein shock.

If such vaccines are used with a full appreciation of their limitations—which of course must on no account be conveyed to the patient—they are sometimes of value in certain cases of chronic bacillary and amoebic dysentery.

Vaccines prepared from cultures taken directly from the ulcer by means of the sigmoidoscope are on a slightly higher scientific plane, but have not been any more successful in the writer's experience.

Diet in recurring dysentery, when acute symptoms have subsided, or in chronic ulcerative colitis. No hot or spiced foods, no strong coffee or tea, and no strong alcoholic drinks are to be taken. All meals should be taken leisurely and if possible quietly; all food should be well chewed. The following suggestions are made for those on European diet :—

Benger's food or Horlick's milk at 7 a.m., or on waking, and again last thing at night.

For breakfast, sieved porridge with milk, lightly boiled or poached eggs, dry toast and butter, with honey or marmite. Weak tea with plenty of milk.

At lunch and dinner, cream soups, steamed fish or chicken, preferably minced or creamed, but may be taken in the ordinary way if well masticated; mutton may be substituted if absolutely necessary, but must be once-cooked and minced; sieved or pureed vegetables, or fresh tender lettuce with olive-oil dressing; milk puddings, soft rice with milk, cold sweet soufflés, or jellies with sieved fruits; toast and butter; and tomato juice.

Weak tea with plenty of milk, and dry toast and butter with marmite at tea time.

Orange juice, and adexolin or some other vitamin concentrates (A and D) should be taken in adequate doses 2 or 3 times a day.

REFERENCES

- ANDREWES, F. W., and INMAN, A Study of the Serological Races of the Flexner Group of Dysentery Bacilli. *Med. Res. Committee Special Rep. Ser.*, No. 42. His Majesty's Stationery Office, London.
- BOYD, J. S. K. (1940) .. Laboratory Diagnosis of Bacillary Dysentery. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **35**, 553.
- LAPPING, D. (1942) .. Chemotherapy in Bacillary Dysentery. *Indian Med. Gaz.*, **77**, 69.

- NAPIER, L. E. (1939) The Ætiology of Tropical Macrocytic Anæmia. *Indian Med. Gaz.*, **74**, 1.
- NAPIER, L. E., and NEAL EDWARDS, Anæmia in Pregnancy in Calcutta. *Indian M. I.* (1941). *Med. Res. Mem.*, No. 33. Thacker, Spink and Co. (1933), Ltd., Calcutta.
- TAYLOR, J. F. (1919) The Rôle of the Fly as a Carrier of Bacillary Dysentery in the Salonica Command. *Med. Res. Comm. Special Rep. Ser.*, No. 40, p. 68. His Majesty's Stationery Office, London.
- TOPLEY, W. W. C., and WILSON, G. S. *The Principles of Bacteriology and Immunity.* (1936). Edward Arnold and Co., London.

FLIES

THE following note on flies and methods of controlling them has been prepared from notes kindly given to me by Dr. D. N. Roy, the Professor of Entomology at the School of Tropical Medicine, Calcutta.

Method of spreading infection. The three ways by which flies spread infection are, (i) by passing ingested pathogenic micro-organisms with their excreta, (ii) by mechanical transfer on the external surface of their bodies, and (iii) by regurgitating the ingested materials.

Species of flies. The house-frequenting flies in India are mostly of two species of *Musca*, *M. vicina* and *M. nebulosa*. It is doubtful if *M. domestica*, the common European species of house-fly, occurs in the plains in India. The common blue-bottle found in the house is *Chrysomya megacephala* and among the flesh flies *Sarcophaga ruficornis* is the most common. In England in addition to *M. domestica*, the lesser house-fly (*Fannia canicularis*), the latrine fly (*Fannia scalaris*), and the large blue-bottle (*Calliphora erythrocephala*) are found in the house. The house-frequenting flies in America are *M. domestica*, *Fannia scalaris*, *Lucilia caesar*, and species of *Sarcophaga*.

CONTROL OF FLIES

The menace of flies may be reduced in three ways, by eliminating or reducing their breeding outside the house, by killing the adults inside the house, and by screening the house, or at least the kitchen, pantry, and dining room.

It is seldom possible completely to eradicate flies, but their number can usually be reduced by proper measures.

For the proper control of each species of fly, an accurate knowledge of its life-history and its habits are essential. While house-flies generally breed in horse manure and garbage, the blue-bottles and flesh flies thrive on the carcasses of animals and birds. Putrefied night-soil forms an important source of origin of the common blue-bottle, *Chrysomya megacephala*, in India and China.

The eye-fly, *Siphunculina funicola*, breeds in moist and contaminated decomposing organic matter, also in the grass thatch bordering the roofs of dwelling houses.

It is needless to emphasize that the use of fly-proof dustbins, the proper removal and disposal of garbage, and a sanitary conservancy system are the first essentials.

Control of breeding. The ways in which fly breeding can be controlled in manure or refuse may be considered under the headings, (i) chemical and (ii) biological.

The **chemicals** for treating manure are potassium permanganate, hellebore, borax, and fluo-silicate.

One drachm of potassium permanganate in 8 gallons of water is sufficient for 10 cubic feet of manure.

Half a pound of powdered hellebore should be mixed with 10 gallons of water, and the mixture allowed to stand for 24 hours; one gallon per cubic foot of the fluid is sprayed on the manure.

One pound of powdered borax for every 16 cubic feet of manure should be mixed with the manure heap by stirring. Borax, when used in such small quantities, has no harmful effect on crops when the manure is later used for fertilizing purposes.

One pound of sodium fluo-silicate in 15 gallons of water is applied to manure until it is fully soaked.

Under this heading, pyrethrum powder might be included, but its use is not economical.

The **biological** method aims at preventing flies from ovipositing, or at destroying their larvæ. By this means, the fertilizing properties of the manure are well maintained. Oviposition can be prevented by covering a well-watered manure heap with turpentine, and it can be reduced considerably by covering the heap with a thin layer of cowdung, which flies do not like. To destroy the larvæ, the manure is packed as closely as possible, and the flies are allowed to breed on the surface. If the manure is watered, the heat of the fermentation will prevent the penetration of the larvæ deeper than an inch or two. The third-stage migrating larvæ can be trapped in various ways when they leave the manure. Hutchinson devised a method of storing horse manure over water, with the object of drowning the migrating third-stage larvæ.

The Indore system of composting night-soil and dry refuse packed in alternate layers and turned over every three days is another example of the biological method of fly control. This device is simple and economical, and has been successfully employed in various places in China and India.

Breeding in night-soil. In India, the potent cause of fly breeding is the careless disposal of night-soil, unprotected open latrines, and the habits of the people in defæcating in fields close to their habitations.

The pans, tubs, or any other receptacles used for the reception of night-soil should be placed in the latrine sub-chambers with well fitted back doors, and the latrine should be sprayed with kerosine oil emulsion or 5 per cent cresol solution every day. The carts for removal of night-soil should be kept clean, and should have well-fitting lids. The night-soil should be removed daily, or at least three times a week. Shallow trench latrines used mainly at *melas* should be filled up with dry grass and leaves and burnt out, or they should be covered with earth, new trenches being used each day. Human fæces should never be buried in trenches less than 4 feet deep.

The type of latrine which completely eliminates fly breeding is the bore-hole latrine (*vide supra*).

Incinerating night-soil and street refuse has not proved as successful as was once thought. The disadvantages are many; it is doubtful if it can be conducted in such a way as to eliminate the breeding of *Musca* in and around the incinerator. Further, it is very wasteful.

Screening. For economic reasons, the screening of the entire house is seldom possible. All foodstuffs including milk should, however, be kept screened. Wherever possible at least the kitchen and the dining room should be screened.

Destruction of adult flies. The two main ways of destroying flies are by poisoning them, or by catching them on a sticky surface, but swatting will in some circumstances be effective. The best **poison** is arsenic, used in the form of sodium arsenite mixed with treacle and water, but serious accidents are likely to occur among children and domestic animals. Formaldehyde is one of the most commonly used poisons against house-flies; a mixture of two drachms of commercial (40 per cent) formalin and two heaped spoonfuls of sugar with lime water to make up one pint is an effective way of attracting flies. Pads of cotton-wool or layers of blotting paper may be soaked in the mixture. As the formaldehyde on exposure quickly turns acid, a much better device is to use the poison in a bottle, and the mouth is closed by means of a platform of absorbent material (blotting paper) from the centre of which a wick of the same material passes down into the fluid.

Other contact poisons have been recommended for use in the house, such as sodium salicylate (used in the same strength as formalin), sodium fluo-silicate in saturated solution. 'Tangle-foot' mixture for making adhesive fly-baits is prepared by heating together (without boiling) a mixture of eight parts of powdered resin and five parts of castor oil or ground-nut oil, until the resin is entirely dissolved. The mixture is applied in a thin layer on papers, or on lengths of stout string, which are suspended in suitable places. The mixture keeps indefinitely in a closed container.

The destruction of adult flies can be accomplished very effectively by the use of pyrethrum sprays as used for mosquitoes.

AMÆBIC DYSENTERY

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Definition.—A dysenteric affection, that is, a condition characterized by ulceration of the large intestine and the passage of numerous stools containing blood and mucus, which may be acute or chronic, and is caused by the protozoal parasite, *Entamœba histolytica*.

Discussion.—There is a very strong tendency in the literature of the present day to give preference to the heading ‘amœbiasis’ and to relegate ‘amœbic dysentery’ to the place of one of the major manifestations of this infection. There is something to be said for this procedure, namely, (i) that it draws attention to the fact that there are many other manifestations of amœbic infection besides dysentery; (ii) that a clinical attack of dysentery is not an essential prelude to these manifestations; and (iii) that considered together these are probably far more important, from a morbidity and possibly also from a mortality point of view, than amœbic dysentery itself. Against it, however, are a number of points; (i) that it is giving precedence to a purely parasitological classification over a clinical one, where this is quite unnecessary; (ii) that, as there are a very large number of amœbæ and several of these infect man, the term might imply infection by any one of a number of species of amœbæ, whereas it only refers to infection by one; and (iii) that, whilst suggesting that the parasite attacks a number of different tissues and causes a variety of pathological changes in these, which is a fact, it also implies that the processes are independent, whereas they are all secondary and dependent on the primary intestinal ulceration.

For these reasons the writer prefers to consider the subject under the heading amœbic dysentery, and to classify the secondary ‘amœbiasis’, including amœbiasis *sine* dysentery, as complications or sequelæ of the primary infection of the bowel wall, which may have been sub-clinical. There are many parallel examples which the writer could quote in favour of his point of view, and, even if there are as many that could be quoted against it, he still proposes to adhere to his view, as he considers that the adoption of this classification will help to rescue tropical medicine from laboratory domination.

Historical.—Amœbic and bacillary dysentery were naturally not differentiated until their respective causative organisms had been identified; there were however strong suspicions, which often amounted to conviction, that the dysentery of the

tropics, which had been long associated in the astute minds of the early clinicians with hepatitis and liver abscess, was a different disease from the jail or asylum dysentery of temperate climates, which was never followed by these sequelæ. As the discovery of amœbæ in the stools of dysenteric subjects preceded the identification of the dysentery bacilli by many years, it is not unnatural that the idea that practically all dysentery, especially in the tropics, was due to amœbæ should become so firmly established that it took many years to eradicate, and the erroneous impression that it is the more prevalent form is even now scarcely eradicated.

In 1875, Losch discovered amœbæ, which were undoubtedly *Entamœba histolytica*, in the stools of a peasant with dysentery who had come from Archangel to St. Petersburg (Leningrad). In 1887, Kartulis in Egypt found amœbæ in a liver abscess and thereby confirmed the previous suspicion regarding the association of the two conditions. In 1891, Councilman and Laffeur described the bowel lesions and first used the term amœbic dysentery. Osler later confirmed all these findings and established the disease in the textbooks with a clear clinical and pathological description. In 1903, Schaudinn differentiated between *Entamœba histolytica* and *Entamœba coli*, but his description was so poor that for a number of years there was still much confusion between the pathogenic and non-pathogenic entamœbæ, to which confusion Musgrave and Clegg working in the Philippines added by claiming that all entamœbæ were pathogenic, or might become pathogenic; they introduced the word 'amœbiasis', but used it in a wider sense than its present application. In 1913, Walker and Sellards in the Philippines demonstrated the pathogenicity of *E. histolytica*, compared with *E. coli*, in a series of human infection experiments. The 1914-18 war gave a great stimulus to the study of this disease, and Dobell, Wenyon, and others clarified the position regarding the differences between these two species, established certain morphological characters as identifying the cysts of *Entamœba histolytica*, and placed the pathogenicity of this species where parasitologists have been satisfied to leave it for the last twenty years.

The present war has again revived interest in this subject. Hundreds of thousands of British and American soldiers are serving in the tropics, so that *Entamœba histolytica* is assured of vast virgin pastures, and it is to be hoped that its behaviour will be carefully studied.

EPIDEMIOLOGY

Geographical description.—The disease has a wide distribution in all tropical and sub-tropical countries; in the temperate zone, its position is anomalous, for the percentage of 'carriers' (*vide infra*) is almost as high as in the tropics, but amœbic dysentery is a rare incident, and when genuine autochthonous cases occur in Great Britain, Canada or even the United States, the incident is usually considered a suitable subject for a special report, which is quoted and requoted in the literature for some years. There are exceptions to this relative immunity to the disease enjoyed by residents in temperate climates, *e.g.* the Chicago epidemics of 1933 and 1934; in the first, 1,400 cases were traced to 400 towns in America amongst visitors returning from this city, 75 per cent of whom had stayed in two hotels (Bundesen, 1934), and in the second, during the great stockyard fire, a hundred firemen and 2,000 spectators who drank sewage-polluted water were affected (Hardy and Spector, 1935). It must also be remembered that the first identified case of amœbic dysentery came from Archangel, which is almost in the Arctic circle.

Epidemic features.—It is essentially an endemic and sporadic disease, and though there are sometimes concentrations of cases indicating a common source of infection (*e.g.* the Chicago incidents reported above) and suggesting an epidemic, true epidemics of dysentery, where the spread of infection can be traced from case to case, are almost always, if not always, bacillary in origin.

Seasonal incidence.—As a general rule, there is no special seasonal distribution in the tropics, sporadic cases occurring all the year round. In special circumstances, for example, where flies are the main disseminators, or when contamination of water supplies is more likely to occur at some special season, there may be a tendency for a concentration of cases. In temperate climates it is usually a summer disease.

Age, sex, and racial incidence.—It occurs at all ages, but is not common amongst children. At the moment the writer has a European child of 4 years in hospital suffering from dysentery with a very heavy *E. histolytica* infection, but he has seen few such cases. Manson-Bahr (1939) claims never to have seen amoebic dysentery in a European child under 10 years old. The commonest ages for this disease are between 20 and 40 years, and the incidence of its sequel, amoebic abscess of the liver, is even more heavily concentrated in this age period. The sexes appear to be equally affected, but liver abscess is less common amongst women. There is little evidence of any racial immunity or susceptibility to infection, but the sojourner and the visitor are certainly more susceptible to the serious complications of this disease than is the native of the tropics. The writer has seen more cases of liver abscess during the last few months in the British military hospitals in Calcutta than he has seen in twenty years in his own hospital in which the large majority of patients are Indians.

ÆTIOLOGY

The causal organism.—*Entamoeba histolytica*, a protozoan of the family Amœbidae, is the causal organism. It is a two-phase organism with an active trophozoite phase and a resistant cystic phase (see plate I, figures 1 to 3). There are other amœbæ which infect man; all of them are probably non-pathogenic, namely *Entamoeba coli*, *Entamoeba gingivalis*, *Endolimax nana*, *Dientamoeba fragilis*, and *Iodamoeba butschlii*.

Morphology.—The trophozoite of *E. histolytica* is an amœboid organism from 15 to 60 microns in the long axis, consisting of a clear ectoplasm and a granular endoplasm; it is greenish in colour, has a nucleus that is ill-defined in the unstained state, and contains ingested red cells.

The trophozoite is extremely active when examined in the fresh state under favourable conditions of temperature. A single large pseudopodium, showing no sharp line of demarcation between ectoplasm and endoplasm, is thrust forward, and into this pseudopodium the rest of the cytoplasm of the amœba appears to flow until the whole organism has moved forward; the process takes place very rapidly.

When the organism has been outside the body of its host for some time, however, it exhibits movements of a different kind; it then becomes stationary, but throws out large hyaline pseudopodia composed of clear ectoplasm sharply differentiated from the endoplasm. The endoplasm contains the nucleus and possibly red blood cells. The nucleus is spherical and vesicular, containing a fine central karyosome; in unstained preparations, it is invisible, in contra-distinction to the clearly visible brighter refractile nucleus of *E. coli*.

The precyst form first becomes immobile, extrudes all food particles, rounds up, and eventually secretes a thin cyst wall.

The cyst thus formed in uni-nucleate, but later the nuclei divide and a quadri-nucleate cyst is formed; it is spherical in shape, 6 to 20 μ in diameter, with a well-defined cyst wall, and contains chromatoid bars.

The amœbulæ, which emerge from the cyst when it reaches the intestine of a new host, are small, actively motile organisms with a clear blue cytoplasm.

The life cycle.—The sequence of events in the life cycle of the amœba is as follows: The cysts are ingested with food or water; they resist the action of the gastric juice and reach the lower end of the small intestine where the intestinal juices dissolve the cyst wall, and a four-nucleated amœba excysts; the nuclei divide and then the amœba itself divides into eight amœbulæ. These remain in the fluid contents of the small intestine and pass through the ileo-cæcal valve; then, escaping from the more solid

and more static contents of the large intestine, they find their way into the crypts of Lieberkühn, where they develop into adult trophozoites, invade the living tissues, and eventually reach a lymph follicle; here they secrete a cytotoxin, there is an inflammatory reaction, and eventually an ulcer forms; in the tissues at the base and in the walls of this ulcer, the amœbæ multiply by simple binary division; amœbæ find their way into the lumen of the gut, where under the sub-optimal conditions they extrude any contained food, become spherical and form a cyst wall; the nucleus divides by binary fission to produce the characteristic four-nucleated cyst, which eventually passes out with the fæces. Once outside the body no further development takes place.

Alternatively, the active amœbæ, during their invasion of the tissues, may find their way into a vein; when this occurs they are carried *via* the portal vein into the liver, where they cause first hepatitis, then multiple small abscesses, and eventually a large liver abscess, according to the number of the invading amœbæ and the resistance (possibly aided by therapy) of the host tissues. At whatever stage this process is halted, the result, as far as the amœba is concerned, is the same; it has reached a dead end. Thus, this invasion of the blood stream must be looked upon as an accident, for it can form no part of the ultimate design of the protozoon; this must be the propagation of its own species, not the destruction of its host, which in this case it may easily bring about. Secondary invasion of the lungs, brain, and skin have been reported a number of times, the skin infection being a result of direct contamination of a skin abrasion around the anus or a colostomy opening.

A single individual will pass many millions of cysts in one day; the number has been estimated as from 300,000 to 45,000,000.

Culture.—Boeck and Drbohlav (1925) were the first workers to find a satisfactory medium for growing amœbæ *in vitro*. The medium generally used is a coagulated serum slant covered with Ringer's solution and egg albumin. The medium thus has a solid and a fluid portion, and the amœba tend to crawl up the slant.

Resistance.—The cysts will survive in sewage for months and for equally long in distilled water; that they will also live in chlorinated water is a fact of some considerable practical and epidemiological importance. Cysts do not however resist drying.

Animal susceptibility.—Kittens are the most susceptible animals; they can be infected by rectal injection of the trophozoite forms, or by ingestion of cysts. Puppies and monkeys can also be infected easily. The disease runs a very rapidly fatal course in kittens and also in some dogs, but in monkeys it is more comparable to the disease in man.

The carrier.—*Entamœba histolytica* is reputed to be an obligatory parasite; that is to say, it has not been found completing its life cycle except in the intestinal tract of man (and of a few, mostly experimental, animals), and it is believed that it cannot complete this cycle without the nourishment of living tissues. If, therefore, a person is passing cysts in his stool, it is evidence that he has some open lesion in the intestinal mucosa, where the amœbæ obtain nourishment and whence they escape. Post mortem, in individuals who had no symptoms of dysentery during life, minute pin-point ulcers containing amœbæ have been demonstrated in the intestinal tract. It is therefore assumed that all persons passing amœbic cysts must at least have such small ulcers in their intestinal mucosa. If the premises are correct, the conclusion appears inevitable, but there are a number of observed facts regarding the incidence of carriers and of amœbic dysentery in different populations that are hard to reconcile. Extensive studies on the percentages of carriers—*i.e.* persons passing *Entamœba histolytica* cysts in their

stools—in different populations have been carried out for many years. Dobell (1921) found 7 to 10 per cent of carriers amongst the civil population in England; Faust (1926 and 1942) found a 20.3 per cent infection rate amongst Chinese and foreigners in Peiping, the incidence in the former being higher, and he places the average incidence of carriers in the United States 'possibly as high as 20 per cent'. In India the incidence has been placed at above 20 per cent by various competent observers. Knowles and Das Gupta found *histolytica* cysts in 10.87 per cent of stools from an unselected population in Calcutta; this finding at a single examination suggests that at least double this number were actual carriers.

Data are available for many countries, but no more need be quoted here; all these observations indicate that in most countries in the world there is a high percentage of carriers, and that though on the whole the percentage is highest in the tropics and in sanitarially backward countries and communities, the differences are not very great; nevertheless, except for rare incidents in temperate countries, amoebic dysentery is confined to the tropics and sub-tropics. The 'carrier' in temperate countries usually gives no history of ever having had dysentery or any other bowel disorder, and, though a host of secondary conditions are attributed to 'amoebiasis' (*vide infra*), the evidence of cause and effect is very often slender.

There is usually a higher percentage of carriers amongst convalescents, and 'contacts', e.g. soldiers returning from tropical countries where the disease has been rife.

Source, route and dissemination of infection.—The resistant cyst is the only infective form, as the delicate trophozoite would obviously not resist the digestive juices, even if it survived long enough to be ingested. A few animals have been found infected in nature—monkeys, rats and dogs—and though it is possible to infect both cats or dogs in the laboratory (*vide supra*), they do not normally pass cysts and are therefore not sources of infection to others. Man is thus probably the only important source of infection. In patients suffering from acute amoebic dysentery, the active trophozoite forms which find their way into the intestinal lumen are swept out with the rest of the intestinal contents, rapidly die, and are incapable of propagating the infection, but in the less acute stages, though there may still be trophozoites, precyst forms have had time to develop into cysts, which are capable of carrying the infection to fresh hosts. The main source of infection is usually considered to be neither the sub-acute case nor the convalescent carrier, but the carrier who has never suffered from a clinical attack of dysentery. However, in the opinion of the writer, the epidemiological and other evidence makes it very questionable whether these symptom-free carriers, especially those that are encountered in temperate climates, can be in any way associated with the dissemination of the disease, amoebic dysentery, though the 'convalescent carrier' and the 'contact carrier' should be regarded with considerable suspicion, and should not be employed as food-handlers.

Invasion is always by the oral route.

The media in which the infection spreads are food and water. The former may become infected by means of flies—but these are not usually considered as important as they are in bacillary dysentery—by food-handlers, or by the contamination of greenstuffs with human sewage used as manure. Water may be directly contaminated by human sewage, as in the historical Chicago incidents (*vide supra*) and it must be remembered that chemical disinfection, e.g. chlorination, does not kill the cysts.

Immunity and susceptibility.—Though there is probably no such thing as complete natural immunity, there is evidence of varying susceptibility in different individuals; in a population exposed to infection, some escape

infection altogether, others harbour the amœbæ and pass cysts for a time without showing any symptoms, yet others suffer from mild dysenteric or diarrhoeal symptoms, while, finally, others will suffer from a serious or fulminating dysentery.

There is not much evidence of individual acquired immunity, one attack appearing to provide little immunity to a subsequent attack; on the other hand, the indigenous inhabitants of the tropics are undoubtedly less likely to develop such serious complications as do sojourners and visitors. Liver abscess is relatively rare in Indians and long-resident sojourners, but is a frequent sequel to amœbic dysentery in the non-immune British soldiers.

There is some evidence of immunological response—as distinct from immunity—as complement fixation occurs when antigen prepared from cultures of *Entamoeba histolytica* is brought in contact with the serum of an infected person (*vide infra*).

PATHOLOGY

The colonic lesions: Site.—The initial ulcers are in a very large percentage of cases in the cæcum; after this, the common sites are the ascending colon, the sigmoid, and the rectum. The secondary ulcers are more widespread, and occur with almost equal frequency in all parts of the large intestine. This is well shown in the diagram below.

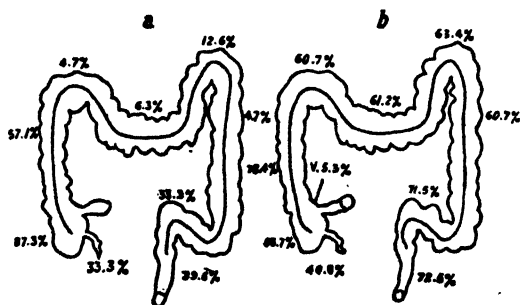


Figure 127 : Showing common sites of amœbic ulcers: (a) Distribution of lesions in 63 cases with only one or two ulcers (probably primary). (b) Distribution of lesions in 186 cases of all types (after Clark, 1925).

The ileo-cæcal valve is sometimes involved, but never the ileum proper.

Mechanism of production.—

The amœbæ find their way into Lieberkühn's crypts, from there they penetrate the mucous membrane, but they do not cause much inflammatory reaction until they reach the submucosa; here they secrete a cytotoxin which acts on the local tissues causing an outpouring of fluid into these tissues, stasis and eventually thrombosis in the capillaries in these areas, and coagulation necrosis. The

amœbæ multiply freely in this necrosed tissue, and may penetrate into, and even through, the muscular layers. There is some question whether they often penetrate further than this during life—for there is evidence that after the death of the host they penetrate in all directions in his tissues—but, post mortem, they have frequently been demonstrated on the peritoneal surface of the intestine. As there is usually a direct connection between this necrotic focus and the gut lumen, a secondary infection occurs and there is infiltration of inflammatory cells and leucocytes. The abscess that is formed is mainly in the submucosa; it has a comparatively narrow opening into the gut lumen, and is usually described as flask-shaped; it undermines and raises up the mucous membrane, which later undergoes a gelatinous necrosis, and eventually sloughs and separates, leaving a deep punched-out ulcer. The tendency is still for the amœbæ to penetrate into the submucous tissues laterally, so that the mucous membrane is nearly always undermined. The extension of the abscess to the muscular coat will often mean involve-

ment of the larger vessels, with resultant severe hæmorrhages, and possibly interference with the circulation, and gangrene of a portion of the gut; gangrene will inevitably lead to perforation and peritonitis.

The **naked-eye appearances** of the ulcers are thus as follows: (a) The first stage is the early round raised area of mucous membrane which at first has a glazed gelatinous appearance with a slight yellow tinge, and later becomes frankly yellow; this is surrounded by a narrow area of hyperæmia, but the rest of the mucous membrane is healthy. (b) The next stage is the large irregular-shaped area of greenish slough, which eventually separates and reveals a deep ulcer with ragged undermined edges; from these, deep lateral sinuses may extend along the submucous layer to join up with similar ulcers some inches away. The mucous membrane covering these sinuses as well as the surrounding mucous membrane may appear quite healthy. (c) In some severe cases, large areas of mucous membrane become gangrenous and separate, and in extreme cases this gangrenous process extends through the whole thickness of the gut wall. (d) Finally, in the healing ulcer, the mucous membrane grows in from the edges and covers the base, leaving a slight depressed area to indicate where the ulcer has been; or (e) a chronic ulcer develops (*vide infra*).

A characteristic of the post-mortem appearance of amœbic dysentery is that ulcers at all stages will be present, those in the cæcum usually being in the later stages of development; and, by means of the sigmoidoscope, the ulcers in the lower end of the bowel may be observed passing through these various stages of development. Sigmoidoscopy is without serious discomfort to the patient, or, except in the extreme cases where there is gangrene, danger to the tissues.

Another type of lesion that is usually associated with milder clinical symptoms, or even the symptom-free carrier state, is one in which there are innumerable minute punched-out ulcers, which give the mucous membrane a 'mouse-eaten' appearance; these ulcers, for some reason (not satisfactorily explained) do not extend further. Simple abrasions of the mucous membrane which are believed to heal up rapidly have also been described, to account for the rarity of the typical 'carrier' lesion.

The **chronic ulcer** has a sharply-defined fibrotic edge, not usually undermined, with a base of granulation tissue lying on the muscular coat; there is a general thickening of the bowel, in which all layers take part. Amœbæ are still present in the deep tissues and, although most of the inflammatory processes are caused by secondarily infecting organisms, healing will not take place while the amœbæ are still there. When the amœbæ are eradicated, the ulcer either (a) heals, leaving a scarred mucous membrane but seldom any serious contractures or a stricture of the bowel, (b) continues as a non-specific ulcerative condition, or, probably quite frequently, (c) heals up and later breaks down again under much the same conditions as does the bacillary ulcer.

Secondary extra-colonic lesions.—The commonest site is the liver; the right lobe is usually affected, the proportion of right to left lobe infections being from 4 to 1 to 20 to 1, according to different observers. The former figure only reflects the fact that the right lobe is much larger than the left, the proportion of the two weights being about 3 to 1; the latter could probably be accounted for by the size and direction of the two branches of the portal vein.

The lesions caused in the liver will depend to some extent on the number of amœbæ that reach that organ, but also, probably to a greater extent, on the natural resistance of the tissues of the liver to this parasitic invasion—livers already overworked or otherwise damaged being much less likely to resist such invasion—and, later, on the presence or absence of secondary

infection. The pathological process may go through the following four stages to reach the final one, or it may be halted at any one of them :—

- (a) *hepatitis*,
- (b) *miliary abscesses*,
- (c) *large 'sterile' abscess or abscesses*,
- (d) *secondarily infected abscess or abscesses*,
- or (e) *an abscess may point and burst through the skin, or into some other organs of tissue (vide infra)*.

The amœbæ may reach the liver in a number of small or large showers, or as a single shower; they are distributed fairly widely in the organ. When they reach a sinusoidal space, they penetrate the endothelial layer and secrete their cytotoxin, causing a local reaction; this is the stage of **hepatitis**. Quite frequently the local response will destroy the amœbæ, but sometimes it fails, and the amœbæ produce a small zone of focal coagulation-necrosis which develops into a **miliary abscess**; resolution may take place at this stage, in which case there is probably complete absorption of these minute abscesses—if not, these abscesses grow and eventually coalesce producing a **single large abscess** which often involves a large part of the lobe; it consists of a necrotic mass of liver cells and cytolysed tissues, but contains little or no true pus. The cavity has an ill-defined ragged wall in which the amœbæ are still active, and it is usually traversed by fibrous bands or trabeculae which the amœbæ have not succeeded in 'lysing'. The abscess may extend and eventually burst into some other organ or tissue, but there is evidence that the process is self-limiting, because very frequently, even without any evidence of secondary infection, the amœbæ will be found to have died, and the abscess may be a completely sterile one. In such circumstances, the necrotic material becomes slowly absorbed, or, if it is large, encapsuled and eventually calcified.

On the other hand, it is not uncommon for the abscess to become **secondarily infected**, via the blood or the bile ducts, or by direct extension, in which case there is an inflammatory reaction, and the abscess cavity becomes filled with pus under tension; it may extend in almost any direction, and will eventually burst; the commonest directions in which a liver abscess will point are—through the abdominal wall and skin, or into the lung, the peritoneum, the peri-renal tissue, the pericardium, or one of the hollow viscera, the stomach, duodenum, or colon.

The contents of the abscess will vary considerably according to the stage it has reached, but the most characteristic is of the consistency and brownish-red colour of anchovy sauce. Microscopically, if it is a sterile abscess, the material aspirated consists of liver-cell debris, a few blood cells, occasionally some pus cells, and Charcot-Leyden crystals. There are seldom any amœbæ, but in an active abscess these can be found by scraping the cyst wall. A secondarily-infected abscess will consist largely of pus and liver-cell debris.

Abscesses in other organs.—Pulmonary abscess, secondary to liver abscess, is comparatively common, but so-called primary lung abscesses have been described. 'Primary' in this instance is meant to indicate 'without the intermediary liver abscess'; it is not a truly primary condition.

Brain and spleen abscesses are not very uncommon, and are always secondary to liver abscess.

Ulceration of the skin.—It is doubtful if the amœbæ could ever penetrate the epidermis, but, once through into the deeper layers of the true skin, they are able to penetrate rapidly, to cause gangrene of large areas



Figure 128 :
Charcot-Leyden
crystals.

of skin, and to produce deep punched-out ulcers. The sites are practically always around the anus or a colostomy wound.

The blood.—There is always a sharp leucocytosis during the acute attack, the count often rising to 30,000 per c.mm. The increase is general and there is not usually a predominantly polymorphonuclear leucocytosis, as one encounters in septic processes, but a general increase in all four main white-cell elements; some writers attach special importance to the eosinophil increase, but in many tropical countries this is 'normally' from 3 to 7 per cent. The leucocyte count returns to normal with the subsidence of the acute symptoms, but it will rise again if there is secondary liver involvement. It does not, however, usually rise very high again, and even 12,000 per c.mm. should be taken as significant; in a frank amœbic liver abscess the white-cell count will sometimes be normal.

There is slight anæmia during the acute stages, which is usually normocytic, but in the chronic stages, where the picture is often complicated by nutritional defects, there may be a marked anæmia and this will usually be macrocytic.

The fæces.—The characteristic amœbic dysentery stool is bulky and offensive, containing 'anchovy sauce' pus, much mucus, and dark red blood often in clots, mixed with fæcal matter at first; later, the stool may consist of little more than 'anchovy sauce' pus and dark blood, and in severe cases gangrenous clots which give it a very offensive smell.

The reaction is acid.

Microscopically, the stool does not present a highly cellular picture; there are many bacteria, yeasts and other organisms, and undigested food debris; the cells that are present are mainly lymphocytes with some polymorphonuclears (both degenerated and possibly only represented by a pyknotic mass of nuclear chromatin, so that their identity may be uncertain), clumped red cells, Charcot-Leyden crystals, and active amœbæ. (For further details and methods of examination see Diagnosis.)

SYMPTOMATOLOGY

Incubation period.—This is usually from 7 to 14 days, but it may be many months, and, if the onset is insidious, the first serious symptoms attributable to the amœbæ may be delayed for many years, when perhaps the patient has returned to a temperate climate.

Clinical types.—There is a wide variation in the symptoms that may occur when the amœba first establishes itself in the colon. For convenience of description, the following types may be visualized but there is no essential difference, except in degree, in the pathology of these various types :—

- (a) *The fulminant attack.*
- (b) *The typical acute attack.*
- (c) *The diarrhœal onset.*
- (d) *Chronic amœbic dysentery.*
- (e) *The latent infection.*

The types are not by any means clear cut, and one type may pass into another, especially if no suitable treatment is given; the chronic type must always have had some prelude, but this may have been a latent infection.

(a) In the severe or **fulminant** attack, there will be very great prostration and toxæmia, with the passage of many bulky and very offensive stools in which there are large gangrenous sloughs, as well as dark blood and pus. There will be severe abdominal pain, often with rigidity of the abdominal wall due to localized peritoneal involvement; later, with the onset of gangrene of a loop of intestine, fortunately a comparatively rare incident, there may be, before the final collapse, a short period when local signs and

symptoms subside and stools decrease, but this is accompanied by a rapidly increasing toxæmia which any physician should recognize.

(b) In the **typical acute** attack, the onset may be sudden with the passage of 10 to 20 stools a day, consisting of fæcal matter mixed with dark blood, mucus and pus. There is a considerable abdominal pain which is at first diffuse, but tends to become localized in the right iliac fossa and then later may become more generalized again; there is not however as much tenesmus as in the attack of bacillary dysentery. The attack is usually afebrile, but there may be an intermittent temperature up to about 100°F.; a higher temperature in an amœbic attack indicates early liver involvement and is not a good prognostic sign; and the pulse rate is usually proportionate to the temperature, but may be increased even in the afebrile attack. There is usually general weakness and loss of appetite. The abdomen is very tender, and the thickened colon can be felt, if the abdominal wall is not too thick.

(c) Perhaps the most common type of onset is the **diarrhœal** onset in which all the signs and symptoms noted above in the typical attack may occur, but will be milder. If suitably treated, the condition usually clears up, but otherwise it may continue in this form for some time, attacks of diarrhœa alternating with periods of constipation, and may pass imperceptibly into the chronic stage, the liver complications often being the first indication of the more serious nature of the condition; or a typical attack with the passage of blood or pus, or even a fulminant attack may develop from this mild beginning.

(d) **Chronic amœbic dysentery.**—For this condition the term chronic amœbiasis seems justifiable. It is, as a rule, secondary to one of the acute or sub-acute types described above, but it is not uncommon to find the condition established in a patient who gives no previous history of dysentery or diarrhœa; however in such cases the infection has obviously been present, though latent, in the patient for some time. The main symptoms are repeated attacks of loose stools, possibly with a little blood and mucus, alternating with periods of constipation, accompanied by slight pain and distinct tenderness in the abdomen, most commonly in the area of the cæcum, descending colon, and sigmoid; the liver is tender, and a thickened bowel will often be felt distinctly through the abdominal wall. There is a muddy or yellowish discoloration of the skin, and a history of loss of weight, indigestion, loss of appetite, and slight general malaise. A large number of secondary symptoms can definitely be associated with this chronic ulceration of the bowel; these include a variety of conditions, in which either allergy or sepsis play a part, skin diseases, pyelitis, rheumatism, eye diseases, all conditions in which a septic focus is reputed to play a part, and nearly all allergic diseases; the ulcers in the colon appear to constitute an open door through which streptococci and other micro-organisms have a ready access to the blood stream, and through which allergens are absorbed.

(e) A latent infection undoubtedly very often occurs without any recognizable clinical symptoms, and from it any of the above clinical forms may develop. This latent infection may be presumed in retrospect from the subsequent development of the chronic condition in a patient who gives no history of any bowel disorder, or it may be observed during life by means of the sigmoidoscope, or post mortem in such a person; when this ulceration is shown definitely to exist, and amœbæ are recovered from the ulcers, it is certainly permissible to use the terms 'amœbiasis' or 'chronic amœbiasis', and to suspect that any of the secondary conditions, enumerated in the last paragraph, from which the patient may be suffering, are due to this condition. But the writer questions the justification of arriving at this conclusion solely on the evidence of the stool and the presence of cysts which

have the morphological appearance of *histolytica* cysts, or of applying the term 'amœbiasis sine dysentery' to these laboratory-diagnosed cases.

COMPLICATIONS

The commonest complications are **hepatitis** and **liver abscess**; these will be considered separately, as, though they are ætiologically linked with amœbic dysentery, they constitute a separate syndrome. Other complications are :—

Hæmorrhages.—The deep sloughing that occurs in the bowel wall often leads to severe hæmorrhage, the signs and symptoms of which are similar to those of any other bowel hæmorrhage.

Peritonitis and perforation.—A localized peritonitis may result in severe cases (*vide supra*). A generalized peritonitis may result from perforation of the bowel wall at the site of a deep ulcer; this is an uncommon accident and seldom occurs except in the case of gangrene of a segment of the colon which subsequently ruptures.

Appendicitis and localized abscess.—Amœbic ulceration in the appendix has been reported fairly frequently; the symptoms are naturally those of appendicitis. If amœbic dysentery is recognized or suspected, it is probably better to give specific treatment for the amœbic infection first, and then, if any localizing signs remain, to remove the appendix. A pseudo-appendicitis from a localized peritonitis due to ulceration in the cæcum is not uncommon, and, in such cases, specific treatment will often obviate an unnecessary operation. Retro-colonic abscesses also may occur, as the results of a leak from, or the frank perforation of, an amœbic ulcer retro-peritoneally. The signs and symptoms will be very similar to those of an appendix abscess, and will often be in the locality of the cæcum, to make the picture more complete. The treatment will be much the same as for an appendix abscess; if a waiting policy is decided upon for other reasons, the time may well be occupied in giving emetine, but if early surgical treatment is indicated, it should not be delayed for this reason.

Cutaneous ulceration.—This has been reported a number of times, the common sites being the neighbourhood of the anus, around a colostomy wound in a case of chronic ulcerative colitis, and at the site of pointing of a liver abscess. Clinically, it is a rapidly-spreading deep ulceration of the skin, with undermined edges and a base of granulation tissue lying on the muscle layer, very painful on pressure, and exuding a purulent discharge. The ulceration is liable to spread with alarming rapidity unless controlled by emetine injections.

Rogers described a condition of **cirrhosis of the liver** which he looked upon as secondary to amœbic hepatitis. His main evidence was the frequency with which the condition was discovered post mortem in Calcutta, in cases in which alcoholic cirrhosis could be excluded, but the writer with more recent local experience, believes that this cirrhosis is more probably dietetic in origin, a sequel to restriction or to mal-absorption of essential food elements, particularly protein.

DIAGNOSIS

The clinical dysenteric attack will have to be differentiated from dysentery from other causes (*see p. 368*).

It is of primary importance that this differentiation should be made in order to ensure the correct treatment (there being radical differences in the treatment for bacillary, amœbic, and other dysenteric conditions), but it is also important from the point of view of prognosis, especially to provide an indication of the complications that are to be expected.

Points of differentiation between bacillary and amœbic dysentery are given in table VI (*p. 413*).

Laboratory diagnosis: Stool examination.—The first point to be borne in mind is that the examination must be made on a fresh stool. Amœbic trophozoites will not be found unless the specimen is absolutely fresh; even cysts begin to degenerate in an hour or so in some stools. In a cold country, it will be necessary to keep the specimen warm, both before and while it is examined, if the activity of the amœbæ is to be maintained, and it is important for proper identification that they should be active. If possible, e.g. in chronic cases, the patient should always go to the pathologist and pass a fresh stool for him to examine, rather than send the specimen to the pathologist. If a stool cannot be passed to order, it is a good practice to insert a rubber catheter into the rectum, rotate it so that the end moves about, and from the 'eye' of the catheter it will usually be possible to obtain a small sample suitable for examination.

The stool must be inspected carefully and its **macroscopical** characteristics noted (see p. 433).

The reaction of the stool should be tested with litmus paper; it will be acid in amœbic dysentery.

For **microscopical** examination, two preparations must be made—(a) in saline and (b) in iodine.

(a) *In saline.* A small portion of stool, if possible a piece containing blood or mucus, is picked out on a platinum loop and transferred to a watch-glass containing a few drops of normal (0.85 per cent) saline; a fine emulsion is made, any mucus present being teased (the emulsion should be such that small print can be read through it); a ring of vaseline is arranged on a clean slide; a drop of emulsion is placed in the centre; and a thin coverslip is placed over it. The slide is placed on the microscope stage—which should be warmed, if necessary—and examined with a 1/8th objective.

(b) *In iodine.* The iodine solution contains iodine—1 gramme, potassium iodide—2 grammes, and distilled water—100 c.cm. (This solution becomes decolorized in a week to ten days and must be made freshly.) A slide is prepared in the same way as with saline.

The saline preparation must be examined immediately, and if there is any delay it must be kept in the 37°C. incubator; the iodine specimen may be kept for some hours.

If the examination is to be thorough, several 'smears' of each kind must be made with samples taken from different parts of the stool.

The general microscopical nature of the stool should be noted, and amœbæ should be looked for and, if found, identified. There should be little doubt about the identity of an active trophozoite of *E. histolytica* when it has once been seen, and it could only be confused with *Entamœba coli* (see table VII) or other entamœbæ, but a sluggish or dead amœba is not unlike an endothelial cell, which may show some amœboid movement. The cysts, which in all but the most acute stages are more readily found than the trophozoites, also have to be differentiated from other amœbic and flagellate cysts, and from *Blastocystis hominis*. About the identity of a single four-nucleated cyst in the saline or in the iodine preparation, there will often be doubt, but, when several specimens are found in each, the doubt will usually be removed; of course, frequently both *E. histolytica* and *E. coli* are present.

When trophozoites are present, there are usually few cysts, and *vice versa*.

The finding of active *E. histolytica* with contained red cells, or of undoubted precysts, is diagnostic of amœbic dysentery. The presence of cysts is also said to be diagnostic of some ulceration, but this may be of the pin-point or shallow type (Faust, 1941), and the writer questions whether it indicates even this when they are found in the stools of permanent residents of temperate countries.

Culture of the fæces for entamœbæ is a laboratory refinement that is certainly worth undertaking if a well-equipped laboratory is available, and it should be done when any special investigation is undertaken to test the efficacy of an amœbicidal drug.

In a convalescent, at least six consecutive daily examinations should be carried out—and found 'negative'—before a patient can be proclaimed as free from infection.

TABLE VII
Important morphological characters of E. histolytica and E. coli

	<i>Trophozoite stage, unstained. E. histolytica</i>	<i>E. coli</i>
<i>Size when rounded</i>	10–30 μ	20–30 μ
<i>Movements</i> ..	Very active in fresh state. Later, finger-like clear pseudopodia thrust out from immobile body.	Very active in fresh state, but rounds up and loses motility very rapidly. As usually seen, is sluggish and with blunt pseudopodia.
<i>Colour and appearance.</i>	Glassy: clear: greenish or yellowish.	Ground-glass.
<i>Inclusions</i> ..	Red cells; usually no bacteria.	No red cells*; bacteria yeasts, starch granules, and even other protozoal organisms.
<i>Nucleus</i> ..	Usually not seen	Usually visible.
<i>Encysted stage, unstained</i>		
<i>Size</i>	6–20 μ	10–33 μ
<i>Shape</i>	Spherical	Spherical.
<i>Cyst wall</i> ..	Thin	Thicker.
<i>Colour and appearance.</i>	Clear: greenish or yellowish	Like ground-glass.
<i>Chromatoid bodies</i> ..	Usually bars with smooth rounded ends: present in most cysts.	Filamentous or splinter-like; seen only in about 5 per cent of the cysts.
<i>Glycogen mass</i> ..	Often very prominent, especially at binucleolar stage.	Sometimes well marked in early stage, but soon disappears.
<i>Nuclei</i>	Usually invisible	Visible.
<i>Encysted stage, iodine preparation</i>		
<i>Cytoplasm</i> ..	Greenish-yellow: smooth and hyaline.	Yellowish-brown: granular.
<i>Chromatoid bodies</i> ..	Indistinct	Not visible.
<i>Nuclei</i>	1 to 4 (rarely 8): minute central karyosome.	1 to 8 (rarely 16, or more); karyosome large and eccentric.
<i>Glycogen mass</i> ..	Yellowish-brown: diffuse	Dark brown: diffuse with indistinct outline.

* Some strains of *E. coli* have been known to ingest red cells in culture, if these are introduced into the medium.

The only other finding to which significance can be attached is the presence of Charcot-Leyden crystals (Acton, 1918). There is little doubt that there is a high degree of correlation between these and *E. histolytica* in stools, but they are not diagnostic.

Complement fixation test.—It is claimed that a 90-per-cent correct diagnosis can be made by means of complement fixation technique with an *E. histolytica* culture extract as the antigen. The results obtained by this test are not entirely consistent, and its specificity is not accepted by all workers.

Other methods.—**Sigmoidoscopy** will aid diagnosis considerably if the appearance of the amœbic ulcer is characteristic, and further a swab-specimen may be taken and examined. A barium enema and a fluoroscopic examination will indicate the extent and position of the ulceration, but on the whole, x-rays are not very helpful in an acute or sub-acute dysenteric attack.

TREATMENT

Historical.—Ipecacuanha has been used in the treatment of dysentery for centuries; it was certainly used in India in 1660. But at this time it was usually given in small doses; in 1846, Parkes revived the interest in this drug and gave it in large doses. In 1866, Macnamara gave the alkaloid, emetine, that had been isolated from ipecacuanha by Pelletier in 1817, by mouth, and from the year 1886 ipecacuanha was given regularly in hepatitis. The emetic properties of emetine were recognized, and ipecacuanha *sine* emetine had a short vogue (Neubert, 1913), but in 1912, Vedder showed that it was the emetine that killed the amœbæ, and that the efficacy of ipecacuanha depended on its emetine content.

In 1912, Rogers demonstrated that emetine could be injected subcutaneously and that it acted as a specific in amœbic dysentery and amœbic hepatitis. He standardized the treatment with this valuable drug that has made such a vast difference to the expectation of life of the white soldier in the tropics.

Later work by Dobell and others cast doubt on the specific action of emetine on amœbæ *in vivo*, and the present opinion is that its action is indirect.

Emetine bismuth iodide (EBI), an emetine compound which it was possible to administer without causing vomiting, was introduced with the idea that a more direct action on the amœbæ in the bowel could be obtained by the oral administration of the drug.

Holarrhena anti-dysenterica (or *kurchi* bark) is an ancient Indian remedy for dysentery. Chopra and others have shown that an extract of this bark has a specific action in amœbic dysentery, though distinctly less than that of emetine.

Many synthetic drugs have been introduced during the last twenty years, e.g. arsenical preparations, such as stovarsol and carbarsone (Reed *et al.*, 1932), iodine compounds, such as yatren (Mühlens and Menk, 1921), and acridine compounds, such as rivanol, for all of which a specific action on the amœba is claimed.

Treatment of the acute attack.—Emetine, one of the most useful and almost certainly the most abused drug ever introduced in the treatment of disease in the tropics, is the mainstay of the treatment of amœbiasis. The fact that there are adults who will tolerate and feel better for 36 one-grain doses of this drug in as many days does not alter the fact that many patients—some of whom did not require the drug at all—have been seriously disabled, and yet others probably killed, by a course of 12 grains in 12 days (*vide infra*). That is to say, as in the case of most drugs, the personal factor is important and it is essential to play for safety.

Directly a diagnosis of amœbic dysentery has been made, a course of emetine should be started without delay. To an adult, six injections of one grain each should be given during the first six days, after which an interval of three to six days should be allowed, and the course repeated; in very mild attacks that respond immediately, three injections in the second course will be sufficient. After this, an interval of at least two weeks should be allowed before any more emetine is given, whatever the circumstances; few cases in which the infection is confined to the bowel will require any further emetine, but the more serious hepatic infections will.

For small women and children, the size of the individual dose of emetine should be reduced proportionately.

Routine.—An ounce of castor oil with 15 minims of tincture of opium should be given on the first day, followed by one grain of emetine hydrochloride given intramuscularly; *the patient should be confined strictly to bed*, and given a light fluid diet mainly consisting of low-fat-content milk, or milk preparations. From the following day, or from the evening of the same day, if the castor oil was given early, he should be given 2 drachms of bismuth carbonate in a glass of water four-hourly night and day, and one grain of emetine intramuscularly 2½ hours after the first daily dose of bismuth. The bismuth may be reduced to thrice daily if the main symptoms—pain and frequent stools—subside, and discontinued altogether in these circumstances when the first course of emetine is complete; otherwise, the bismuth should be continued through the second course of emetine.

After this, in those cases in which there are cysts still present in the stools, and/or in which there are still some residual symptoms, carbarsone should be given in two daily doses of 0.25 gramme for 10 or 15 days, whichever is indicated by the progress of the patient. When carbarsone is being taken, a dose of salts should be given to ensure complete evacuation of the drug, as otherwise its action is likely to be cumulative. Or, for this immediate follow-up course, emetine bismuth iodide (EBI) is favoured by some workers. This is given in 3-grain doses, for a week to ten days, in hard gelatin capsules, or as salol-coated pills, taken at night two hours after a light evening meal and preceded if necessary by some sedative mixture, phenobarbitone, 2 grains, or tincture of opium, 15 minims. These precautions are necessary to stop vomiting.

The treatment of the acute attack can be rounded off by prescribing liquid extract of kurchi, a drachm thrice daily for three weeks to a month, and some form of ispaghula (*Plantago ovata*) to be taken at night to regulate the bowels, as great care should be taken to avoid constipation.

As far as possible, progress should be checked by sigmoidoscopy, but it must be remembered that most of the lesions are likely to be out of reach of the sigmoidoscope.

The vast majority of cases will respond to this course of treatment. Those who do not must be looked upon as chronic cases and treated accordingly (*vide infra*).

Diet.—As stated above, at first the diet must be light and fluid, lime whey, albumin water, skimmed milk, citrated milk, or Benger's food, fruit juice and glucose, marmite, and chicken broth, and then light solids, milk puddings, egg dishes, and boiled fish. Meat, fat and any food with much roughage should be avoided, as also should alcohol. A semi-vegetarian dietary, which does not contain too much roughage, should be maintained for some time, as this tends to keep the large bowel content alkaline.

Toxic effects of emetine.—The most disastrous consequences may result from the ill-advised administration of emetine. These results are the more frequent and serious on account of the dramatic early favourable effects on the patients who are being poisoned. During the 1914–18 war, the writer saw many examples of inexperienced medical officers giving two and even three grains of emetine daily for long periods and literally killing their patients, of whose fate they were often quite unaware on account of the frequent evacuations from hospital that are inevitable in war-time. In the subsequent years, he has seen athletic young men's hearts disorganized for years through the failure of their medical advisers to realize that they should advocate strict rest in bed during the whole time a patient is taking emetine.

The most dangerous and important effect is on the heart in which it produces myocardial degenerative changes and alterations in conductivity, with a fall of blood pressure, cardiac irregularity, and acute dilatation as the result of any undue effort. It also may cause acute mental depression, neuritis, myositis,

changes in the skin and nails, and diarrhoea, which last-named is likely to be attributed to the dysenteric condition.

Other symptoms.—Abdominal pain may be severe and interfere with rest at night; in the latter case, morphia is certainly indicated for a night or so until the treatment takes effect, but minor degrees of discomfort can be aided by hot fomentations or turpentine stupes.

Tenesmus is less common but can be relieved in the same way as in bacillary dysentery (*vide supra*).

Treatment of chronic amæbic dysentery.—This presents one of the major problems of tropical medicine. The action of emetine is specific if given early, and every effort should be made to give an efficient course in good time. However, in the chronic stages, the action of emetine is very disappointing, and in the absence of hepatitis, it is questionable if it should be employed at all.

At this stage, drugs that have a direct action on the intestinal mucosa appear to act better than emetine, and therefore emetine bismuth iodide, given as indicated above, is of value. However, in the writer's experience, carbarsone is the most useful drug at this stage, provided that there is no hepatitis or cirrhosis; other drugs, such as yatren and its English equivalent chiniofon, diodoquin, vioform, and rivanol (an acridine compound) all have their special advocates, and it may be advisable to give each a trial in an obstinate case, but even then a cure may not be effected until medicated bowel washes are also given.

Chiniofon (yatren) is given in keratin-coated pills of 0.25 gramme (about 4 grains) each, one pill three times on the first day, the dose being increased to two pills and then three pills daily on the two succeeding days, if it can be tolerated, for ten days.

Vioform, also best given in the form of keratin-coated capsules, and diodoquin are given in doses of 0.5 gramme three or four times a day. In the case of the former, it is best to limit the course to 10 days, as toxic effects have been reported, but the latter can be continued safely up to a fortnight more.

For medicated bowel washes, chiniofon (20 c.cm. of a 2.5 per cent solution) is the most popular, and considerable success has been claimed with it by some workers, although the writer has been less fortunate. Manson-Bahr (1939) uses a combination of EBI by mouth and chiniofon per rectum, which he claims is almost infallible.

Other bowel medicaments have been used with success, *e.g.* rivanol which is recommended in a strength of 1 in 2,000, but the writer has usually found that silver nitrate solution combined with the administration by mouth of some 'specific' drug, *e.g.* carbarsone, is as good as the far more expensive yatren.

All medicated bowel washes must be preceded by a 2 per cent sodium bicarbonate enema, which the patient retains for about 10 minutes and then passes as completely as possible. After this, the medicated retention-enema is run in slowly—about 8 ounces is usually sufficient for the patient to retain comfortably; he should retain this as long as possible, up to 8 hours in the case of yatren (2.5 per cent). Silver nitrate is given in increasing strength, from 1 in 750 up to 1 in 250 or even stronger. If the enema causes much pain, it can be washed out immediately with normal saline, but if not, it should be retained as long as possible, up to about 5 hours. The patient should lie on his left side whilst the wash is being run in, and should then assume the knee elbow position to allow it to run well up into the transverse colon and, one hopes, beyond.

It is usually necessary to keep up the bowel washes for at least a fortnight before much benefit will be apparent, except some soothing effect

which is often an almost immediate result, and they may have to be continued daily for a month or more. Later, as improvement is established, the washes may be reduced to one every other day.

After this course, extract of kurchi and ispaghula (*vide supra*) should be prescribed for at least two months.

Vaccines.—In chronic ulcers, which are mainly maintained by secondary infection, but in which the amœbæ are still active, a vaccine, preferably made from an organism obtained directly from the ulcer by means of the sigmoidoscope, is sometimes helpful (*see p. 412*). When the secondary bacterial infection is overcome, the tissues are apparently better able to deal with the amœbic infection.

Diet.—Great care must be exercised in advising patients about their diet, in these chronic bowel conditions. As much emphasis should be laid on what the patient is going to take, as on what articles of diet he should avoid, and this will depend on his normal dietary habits about which the doctor should question him carefully, if he does not already know them. The thoughtless recommendation of restricted diet may lead to a patient's eventually suffering from specific dietary deficiencies, if not general starvation, which will help to maintain the bowel lesions. The diet must contain the full quota of calories suitable for a person at rest, and also all the vitamins and essential minerals. Meat, excess of fat, coarse vegetables and fruits, spices, condiments and pickles, very hot and very cold substances, strong tea or coffee, and alcohol, should be avoided.

As secondary infection of the ulcers is an important factor at this stage, it may be useful to attempt to influence the intestinal flora by giving bulgaricized milk (in India the ordinary *dahi* will serve the same purpose), with or without the addition of lactose, a heaped tablespoonful first thing in the morning.

PREVENTION

Man is apparently the sole source of infection, so that proper faecal disposal and sewage treatment are the most important measures. It should be remembered that the cysts—the infective form—will survive in a septic tank for some months.

Water is not usually incriminated—although it was the vehicle in at least two historic epidemics; however, it cannot be ignored, as ordinary chemical methods of water sterilization will not destroy cysts, although almost any form of filtration will. The writer believes that more attention should be paid to water as a source of this infection.

Uncooked food, especially greenstuffs in the growing of which human manure may have been used, and food exposed to contamination by flies are probably the commonest sources of infection, and preventive measures should be adopted against these, especially against flies.

The isolation of persons with acute dysenteric symptoms is of little value as a preventive measure, as such persons pass few cysts; it is important however that, when they become convalescent, they should be followed, examined periodically, and, if they are found to be passing cysts, treated.

Most of the measures for prevention are thus general sanitary measures, and the only special preventive measure is with reference to carriers (*quod vide*). In institutions and households a systematic stool examination should be carried out amongst all food-handlers, and the 'carriers' weeded out and treated. What is at present impeding legislation in the matter of enforcing such precautions in public eating places is the uncertainty regarding the importance of the 'cyst-passer' in temperate

countries, but the measure should be rigidly enforced in the case of the convalescent carrier, especially in tropical countries.

PROGNOSIS

This will depend on how soon treatment is undertaken and on its efficacy. It is impossible to give figures, but an initial attack is very rarely fulminant. Almost all the deaths that occur as a direct or indirect result of amoebic dysentery are due to neglect of treatment in the early stages. There is however a small percentage of cases in which the symptoms persist for months and even years, despite (ordinarily) efficient measures.

With the establishment of hepatic complications the prognosis becomes graver (*vide infra*).

REFERENCES

- ACTON, H. W. (1918) .. The Significance of Charcot-Leyden Crystals in the Fæces as an Indication of Amoebic Colitis. *Indian J. Med. Res.*, **6**, 157.
- BOECK, W. C., and DRBOHLAV, J. (1925). The Cultivation of *Entamoeba histolytica*. *Amer. J. Hyg.*, **5**, 371.
- BUNDESEN, H. N. (1934) .. The Chicago Epidemic of Amoebic Dysentery in 1933. *Pub. Health Rep.*, **49**, Pt. 2, 1266.
- CLARK, H. C. (1925) .. The Distributions and Complications of Amoebic Lesions found in 186 Post-mortem Examinations. *Amer. J. Trop. Med.*, **5**, 157.
- COUNCILMAN, W. T., and LAFLEUR, H. A. (1891). Amoebic Dysentery. *Johns Hopkins Hosp. Rep.*, **2**, 393.
- DOBELL, C. (1921) .. A Report on the Occurrence of Intestinal Protozoa in the Inhabitants of Britain with Reference to *Entamoeba histolytica*. *Med. Res. Council Special Rep. Ser.*, No. 59. His Majesty's Stationery Office, London.
- FAUST, E. C. (1926) .. Parasitic Infections and Human Disease in China. *Arch. Path. and Lab. Med.*, **2**, 223.
- Idem* (1941) .. Amoebiasis in the New Orleans Population as revealed by Autopsy Examination of Accident Cases. *Amer. J. Trop. Med.*, **21**, 35.
- Idem* (1942) .. The Prevalence of Amoebiasis in the Western Hemisphere. *Amer. J. Trop. Med.*, **22**, 93.
- HARDY, A. V., and SPECTOR, B. K. (1935). The Occurrence of Infestations with *E. histolytica* Associated with Water-Borne Epidemic Diseases. *Pub. Health Rep.*, **50**, Pt. 1, 323.
- KARTULIS, S. (1887) .. Zur Aetiologie der Leberabscesse. Lebende Dysenterie-Amöben im Eiter der Dysenterischen Leberabscesse. *Centralbl. Bakt.*, **2**, 745.
- MANSON-BAHR, P. H. (1939) .. *Dysenteric Disorders*. Cassell and Co., Ltd., London.
- MUHLERS, P., and MENK, W. (1921). Ueber Behandlungsversuche der chronischen Amöbenruhr mit Yatren. *Münchener med. Woch.*, **68**, 802.
- NEUBERT (1913) .. Ueber die Wirkung von Uzara und geronnener Milch bei Darmerkrankungen. *Arch. Schiffs- u. Trop.-Hyg.*, **17**, 840.
- REED, A. C., ANDERSON, H. H., DAVID, N. A., and LEAKE, C. D. (1932). Carbarsone in the Treatment of Amoebiasis. *J. Amer. Med. Assoc.*, **98**, 189.
- ROGERS, L. (1912) .. Sixty Cases of Amoebic Dysentery Illustrating the Treatment by Ipecacuanha and Emetine respectively. *Indian Med. Gaz.*, **47**, 421.
- ROGERS, L. (1912) .. The Rapid Cure of Amoebic Dysentery and Hepatitis by Hypodermic Injections of Soluble Salts and Emetine. *Brit. Med. J.*, **i**, 1424.
- SCHAUDINN, F. (1903) .. Untersuchungen über die Fortpflanzung einiger Rhizopoden. *Arch. Kaiserl. Gesundheits-Amte*, **19**, 547.

- VEDDER, E. B. (1912) An Experimental Study of the Action of Ipecacuanha on Amœbæ. *Trans. Second Biennial Congress, Far Eastern Assoc. Trop. Med.*, Hongkong, p. 87.
- WALKER, E. L., and SELLARDS, A. W. (1913). Experimental Entamœbic Dysentery. *Philippine J. Sci.*, **3**, 253.

AMÆBIC HEPATITIS AND LIVER ABSCESS

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Historical.—The association between dysentery and liver abscess has been suspected since the days of Galen, and some of the earliest observations of amœbæ, namely those of Koch, Kartullis, and Osler, were made in material from liver abscesses. But there was still a school of thought (*e.g.* Andrew Duncan at the London School of Tropical Medicine) which denied the general association, mainly, it appears, on account of failure to find the amœbæ in the pus of the larger abscesses. In 1886, Norman Chevers and Maclean advocated ipecacuanha, then used in the treatment of amœbic dysentery, in hepatitis to prevent abscess formation. Between 1902 and 1907, Rogers definitely established the relation between amœbic dysentery and liver abscess by showing that in a large percentage of cases amœbæ could be recovered from the walls of these abscesses; he also suggested that some specific medicinal treatment, *e.g.* ipecacuanha, the use of which he revived, might be used instead of the unsatisfactory surgical treatment then in vogue. In 1912, he introduced the emetine treatment for hepatitis and amœbic abscess.

Ætiology and epidemiology.—The cause of these conditions is the presence of amœbæ in the liver which they reach *via* the portal vein from an ulcer in the colon (*see* p. 431); in patients with liver abscess, a clear history of past dysentery is obtained in only 60 to 90 per cent of instances, according to the experience of different observers, and in little more than 50 per cent are amœbæ found in the stools at the time the abscess is diagnosed.

Further, in the epidemiology of the conditions there are many unexplained facts; for example, that amœbic abscess does not occur in temperate climates though amœbiasis is common (*vide supra*), that it is ten to twenty times more common amongst visitors and sojourners in the tropics than amongst the native residents, and that it is ten times more common in men than in women.

One explanation is that alcoholic excesses predispose to these conditions, but this is not a sufficient explanation of the relatively high incidence in India at the present time amongst the British troops whose indulgence in alcohol is at least limited by opportunity even if not by inclination, and of the rarity amongst certain hard-drinking groups of more acclimatized Europeans. It is a subject that should be removed from the fervent atmosphere of prohibitionists' propaganda into the cold light of statistical research.

The writer considers that there are indications that the higher incidence may be correlated with a heavy meat diet, and/or with lack of the immunity produced by previous experience, but he admits that his data would withstand statistic analysis no better than would that of his predecessors.

Amœbic liver abscess does not occur in children, and is rare below the age of 20 years.

Amœbic hepatitis is probably a very much more common condition than is indicated in the literature on the subject, in which figures are based mainly on the cases in which liver abscess subsequently develops.

SYMPTOMATOLOGY

Each of the four stages in the pathological process (*vide supra*) of the invasion of the liver has its corresponding clinical picture, though it is of course not possible to be dogmatic as to the exact signs and symptoms that will be produced at each stage.

The mild form of amœbic hepatitis is indicated by malaise, a low irregular but fairly constant fever, and a feeling of heaviness and constriction below the diaphragm, or actual pain in the liver region; the liver will be enlarged and tender; and the white cell count slightly raised, 10,000 to 12,000 per c.mm. Treatment for hepatic congestion, *e.g.* calomel and sodium sulphate or mercury pill, will not usually be sufficient, but a very marked improvement will follow a few injections of emetine.

The evidence that such an attack is amœbic hepatitis is not conclusive, and the improvement caused by emetine, though suggestive, is not confirmatory, as the writer believes that this drug often has a non-specific effect on hepatic congestion, but in patients who later develop liver abscess a history of such attacks is very common, and from a pathological point of view it is extremely probable that a small 'shower' of amœbæ would cause a minor degree of hepatitis that the natural tissue resistance in an undamaged liver might well overcome. Rogers has used the term *pre-suppurative* stage for this, but this term is avoided here, because it seems to indicate inevitable suppuration, which, even in the untreated patient, is not justifiable.

In the next stage, in which there is **miliary abscess** formation, the clinical picture is likely to be both more severe, and more chronic; the temperature may develop a more hectic character and be accompanied by severe sweating. The liver is usually enlarged and tender, but not continuously so, especially in the more chronic forms, when the temperature chart may show periods of intermission. The leucocyte count is now definitely raised, being usually 15,000 to 18,000 per c.mm. with a slight predominance of polymorphonuclears. Here again *pre-suppurative* is an inappropriate adjective as suppuration is almost certainly occurring in small circumscribed areas, where periods of subsidence of activity alternate with

periods of reactivation and advance. At this stage also, emetine will often control the condition, but it must be given for a longer time.

The stage of **liver abscess** will usually present a more definite clinical picture, but nevertheless there are many cases that show few or none of the classical signs and symptoms, and cases are on record in which an abscess has suddenly burst, *e.g.* into the lung, without any previous record of ill health.

The patient may give a history of previous illness that would correspond with the earlier stages referred to above, but on the other hand, the onset may be sudden, as the symptoms are more associated with the body's reaction to the invasion than with the invasion itself which may have taken place rapidly and unimpeded. However, he will usually be seriously ill; he will have a grey look with a sub-icteric tinting of the skin and sclerotics, but not often actual jaundice. The onset of fever may be sudden, with a rigor, or it may develop more gradually into a hectic remittent, occasionally an intermittent, or even a high continuous, fever with severe sweating. His pulse will be rapid; he may complain of dysphagia, indigestion, severe liver pain, which is usually stabbing in nature and very often referred to the right shoulder, and an irritable cough. The leucocyte count will be 20,000 per c.mm. or more, but this is not a constant finding (see figure 130), and a normal or a lower count does not exclude liver abscess especially in an Indian patient. The liver is always enlarged and tender, but the rectus may be so rigid that this is difficult to feel. Pain will be caused when the thorax over the liver area is pressed between the hands; there will also be tenderness in the inter-costal spaces, and there may be some inter-costal oedema.

Other physical signs will depend on the size and position of the abscess. If it is in the left lobe or in the palpable portion of the liver below the costal arch, it may produce a local bulge in the abdominal wall which it is possible to recognize as an abscess; it may be tense, but it is more usually soft and can in any case readily be distinguished from a hydatid cyst by the absence of the characteristic thrill of the latter.

There will often be râles or friction sounds at the base of the right lung.

X-ray examination will be invaluable, as the commonest site is in the right lobe just below the diaphragm. There will usually be definite limitation of movement of the diaphragm on the right side; it may be much higher than normal, or it may show a definite localized bulge. There may be evidence of the involvement of the lung at the base, and the heart may be pushed over to the left side (see plates XIII and XIV).

The abscess may point and eventually rupture externally, either laterally through the chest wall, or below the costal margin; or it may rupture internally in a number of directions. Probably the most common route taken by the abscess is to rupture into the lung or bronchus; this can sometimes be foreshadowed by suggestive physical signs and/or symptoms referable to the lung or pleural cavity, or by x-ray. When the abscess ruptures into the lung, the contents are immediately coughed out, and the patient may die of dyspnoea, or of shock, but, if he recovers from the immediate effects, complete recovery is very common. The walls of the abscess collapse and close the opening and sepsis may be obviated.

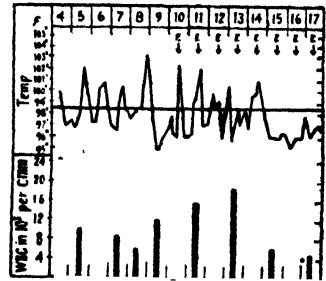


Figure 130 : Shows the inconsistency of the leucocytosis in liver abscess; the condition responded to emetine treatment.

PLATE XIII
Amæbic liver abscess



Fig. 1.—Showing the high raised right dome of the diaphragm; it has an unusually clean-cut outline. The heart is pushed over to the left. Two pints of pus were obtained by aspiration.

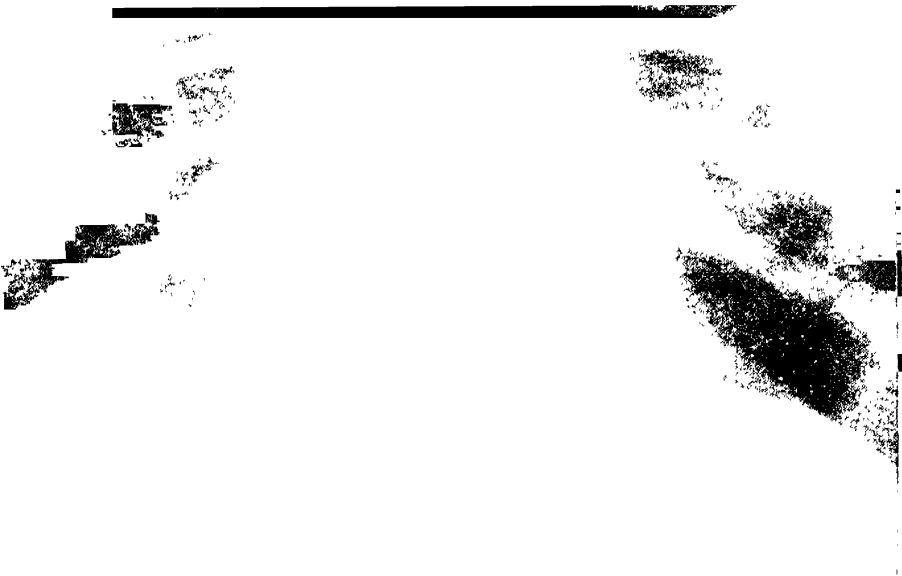


Fig. 2.—Showing a local dome-shaped swelling superimposed on the right dome.

PLATE XIV
Amœbic liver abscess

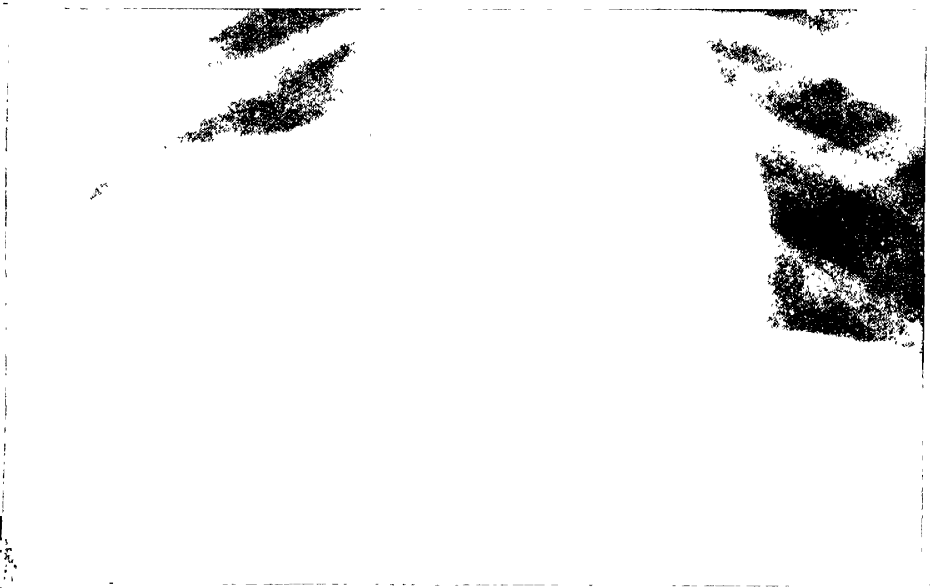


Fig. 3.—Showing another high right dome.

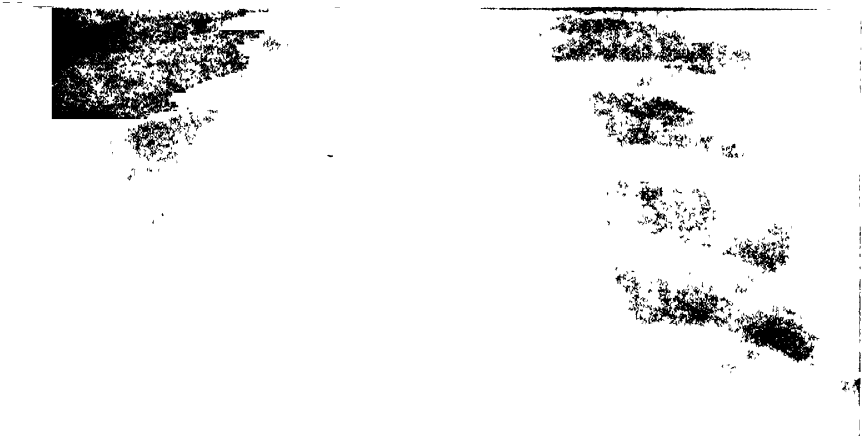


Fig. 4.—In this case the diaphragm is scarcely raised, but the lung is apparently involved. Two days before this was taken the patient coughed up over a pint of pus; he made an uninterrupted recovery.

Rupture into the pleural cavity is far less common. Other common directions are into one of the hollow viscera, stomach, duodenum or large intestine. Rupture into the pericardium, the gall-bladder, the pelvis of the kidney or into the loose perinephric tissue, and into the peritoneal cavity has been reported (see figure 131).

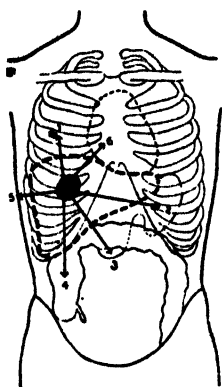


Figure 131 : Diagram showing some of the directions in which a liver abscess may burst.

1. Into the lung, or pleural cavity.
2. Into the stomach.
3. Into the duodenum.
4. Into the cæcum.
5. Through the skin.
6. Into the pericardium.

Diagnosis.—If the patient gives a history of living in the tropics under conditions in which he is likely to have acquired an amœbic infection, not too much attention should be paid to whether he has actually suffered from amœbic dysentery, or whether he has the infection at the moment, though either fact would add weight towards a positive diagnosis. **Clinical and radiological** evidence has been discussed above, and the response to emetine has been mentioned and will be discussed again under treatment, but it should be emphasized here that at any stage the **therapeutic test** with emetine is of value; in the early stage of simple hepatitis, a definite response will usually follow three daily injections; if it is suspected that the stage of miliary abscesses has been reached, at least six should be given; and even when there is a large abscess, some distinct clinical improvement will usually follow six injections but it may be advisable to persist up to nine. The **blood picture** will give additional evidence, but it must be remembered that the leucocytosis is neither as constant nor as high as one might expect. The final court in the diagnosis of liver abscess is an **exploratory puncture**.

Technique of exploratory puncture.—A large serum syringe with a needle of moderate bore (about no. 9), not less than $3\frac{1}{2}$ inches long, is used. A local anæsthetic should be injected at the point selected. The needle is inserted either at a point where the abscess appears to be pointing, or, when there is no such indication, in the 8th interspace in the mid-axillary line, and thrust into the liver substance at first in a slightly upward and forward direction towards the right cupola of the diaphragm; if no pus is obtained, the needle is partly withdrawn, and pushed in again in another direction; a third or even a fourth attempt may be made, but if these fail it must be assumed that there is no large abscess present. If the anatomy of the liver is visualized, if common sense is used, and if care is taken to avoid the gall-bladder and not to thrust the needle in to a depth greater than $3\frac{1}{2}$ inches in any direction, the procedure is a reasonably safe one. From time to time, the plunger is withdrawn, and, if an abscess is entered, the syringe will fill with pus, either a chocolate-brown, the typical anchovy sauce, or ordinary yellow pus. In some cases it is very viscid and it is only possible to obtain very little through the ordinary exploring needle; it is advisable to detach the syringe and pass in a stylet to remove any blockage. Amœbæ are rarely found in the pus thus withdrawn, and therefore the direct examination of the fluid will give little information, but a culture should be made, as the subsequent treatment of the case will depend on whether or not the abscess is already secondarily infected. (In an active abscess amœbæ are present, but are confined to the walls of the abscess cavity, and will therefore only be found in the last few ounces of pus when the abscess is later aspirated: *vide infra*.)

Differential diagnosis.—In view of the very considerable variability in the signs and symptoms of amœbic hepatitis and liver abscess, and the possible absence of any, especially in the early stages, an adequate discussion on this subject would cover half the field of internal medicine. In

these circumstances, it will be best to give a short classification, with a few examples, of the diseases that may simulate, or be simulated by, amoebic hepatitis and liver abscess.

Febrile conditions. **Long fevers.**—Enteric, tuberculous, and *Bacillus coli* infections, the Pel-Ebstein syndrome, undulant fever, and kala-azar.

Short fevers.—Malaria, relapsing fever, rat-bite fever, and leptospirosis.

In most of these conditions either rigors or profuse sweating will sometimes, if not usually, occur, and either of these symptoms will heighten the similarity.

Hepatic enlargements. **Generalized.**—Hepatic congestion, active or passive, infective hepatitis, kala-azar, bilharziasis, early cirrhosis, syphilis, tuberculosis, actinomycosis, leukæmia, and tularæmia.

Localized.—Hydatid cyst (suppurating or otherwise), gumma, carcinoma, and pyæmic abscesses.

Extra-hepatic conditions.—Pneumonia, basal pleurisy and empyema; cholecystitis and suppurative cholangitis; pyelonephritis, perinephric abscess, and sub-phrenic abscess; appendicitis with complications.

TREATMENT

General.—The patient must be confined to bed whenever a definite diagnosis of amoebic hepatitis or liver abscess is made. He should be given a light diet, mainly of milk and milk products during the febrile bouts, with plenty of fruit juice and glucose to drink.

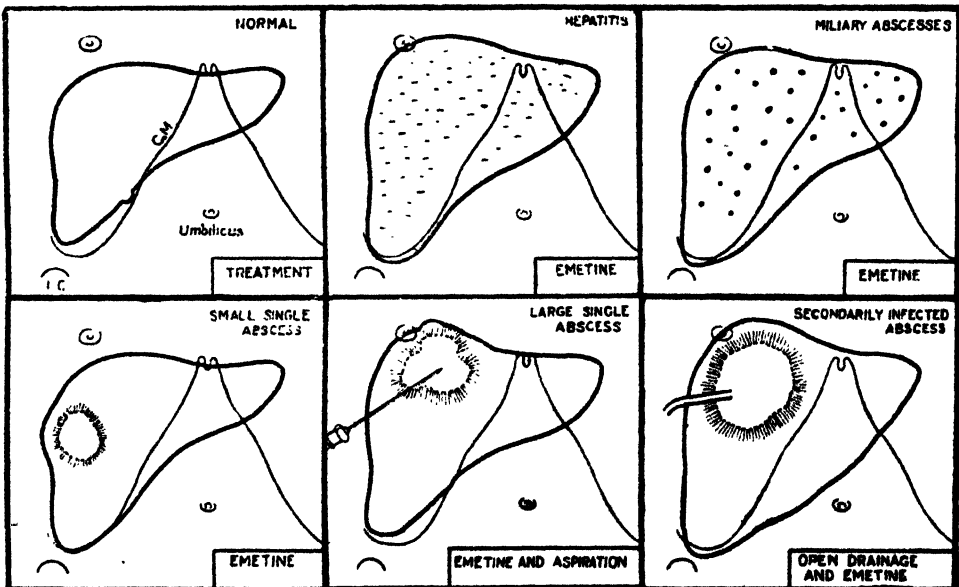


Figure 132 : Showing five stages of liver involvement and the treatment of choice in each case.

Pain should be relieved by local applications, hot fomentation or anti-phlogistin. Sleep should be ensured by bromide and aspirin, phenobarbitone, or Dover's powder.

The bowels should be kept open, if necessary, with magnesium sulphate, liquorice powder, or a mercury and aloes pill (*see* p. 51).

In severe cases, a daily dose of intravenous glucose will be beneficial.

Specific.—It is in the hepatic complications of amoebic dysentery that emetine is of the greatest value, and, in amoebic liver abscess, the combined

treatment of emetine administration with aspiration is a very great advance on the previous method of open operation in which the death rate was always above 40 per cent.

At every stage of the invasion of the liver by amœbæ, emetine is of value. Some indication has already been given of what may be expected from emetine administration.

While in the earliest stage of hepatitis, three one-grain injections will usually cause a definite clinical improvement, it is well to add another three injections when one is satisfied as to the specific nature of the infection.

In the early suppurative stage, two courses of six injections each (or nine injections followed by three are preferred by some physicians, see figure 133) with a short interval between them, are usually necessary.

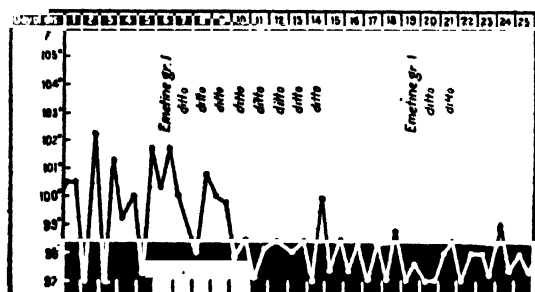


Figure 133 : Showing a rapid response to emetine; the process had probably reached only the miliary-abscess stage.

Aspiration.—Even when a large abscess has obviously formed, it is quite often possible to control the condition by emetine alone without aspiration. However, if the evidence points to a large abscess, or if preliminary treatment, while perhaps controlling the fever to some extent, has obviously not completely halted the pathological process, it will be as well not to postpone aspiration any longer. If emetine has not

already been given and if the urgency of the occasion seems to permit, it should be given before the operation, if not, then after operation, until the fever is controlled or 12 injections have been given. In a serious condition like this certain risks (see p. 439), which might be unjustifiable in other circumstances, have to be taken with emetine dosage (e.g. cases of figures 134 and 135).

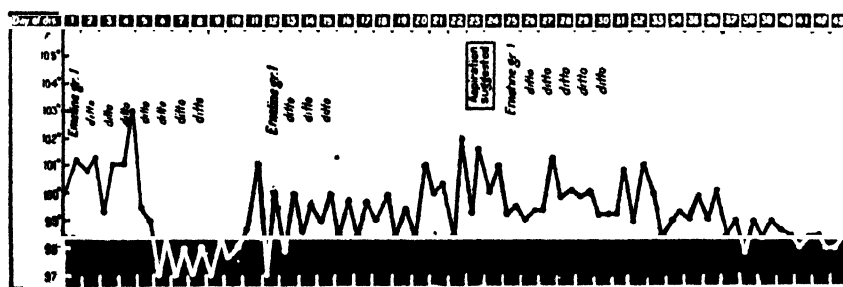


Figure 134 : Showing delayed response to an 'overdose' of emetine (see text).

In the case of which the temperature chart is shown (figure 134), aspiration was seriously contemplated as his temperature had not fallen after 12 emetine injections, but instead, emetine was given again, and aspiration obviated. In another case (figure 135), both aspiration and emetine were necessary, but the patient eventually recovered.

Technique of aspiration. After a successful exploratory puncture (*vide supra*), the cannula of Potain's aspirating apparatus with the trocar in position is inserted along the tract along which the exploring needle passed, and, as nearly as possible, to the same depth. The stylet is then withdrawn and the negative pressure from the exhausted Potain's bottle turned on. If the point is in the cavity, pus will drain into the bottle. No more than two pints should be withdrawn at one sitting. It may be necessary to replace the stylet periodically if the cannula becomes blocked.

OTHER PROTOZOAL AND METAZOAL DYSENTERIES AND DIARRHŒAS

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FLAGELLATE DIARRHŒAS : GIARDIASIS

Discussion.—The commonest intestinal flagellates are *Trichomonas intestinalis* and *Chilomastix mesnili* which infest the cæcum and large intestine, and *Giardia enterica* (*Giardia intestinalis* or *lamblia*) which is found in largest numbers in the duodenum and small intestine. The only flagellate about the pathogenicity of which there seems to be any unanimity of opinion is *Giardia enterica*. It is usually agreed that the other flagellates are found more frequently in an unhealthy stool than in a formed one, but this does not mean that the flagellates cause this condition; on the contrary, the condition of the bowel probably encourages the flagellates to multiply, so that they are always found in greater numbers. Their presence, if known to the patient, may encourage a neurasthenic subject to take an unhealthy interest in his bowel fauna, but there is little evidence of their pathogenicity.

The writer has until recently always questioned the pathogenicity of *Giardia enterica*, and, except in children in whom he was satisfied that it did cause diarrhœa, he was inclined to place it in the same category as the other flagellates. During the last few years, since, in fact, the introduction of a specific treatment for this infection, all his doubts have been dispelled.

As it would be absurd for the writer to describe a symptomatology which he does not believe exists, he will make no further reference to the other flagellates, and will discuss only giardiasis.

Historical.—Leeuwenhoek discovered the parasite whilst using his primitive microscope, in 1681. It was rediscovered as a human parasite by Lambl in 1859, and given the name *Lambia intestinalis*, but as another species of the genus had previously been described and given the generic name *Giardia*, Lambl's parasite

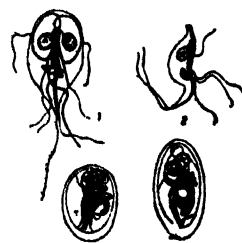


Figure 136: *Giardia enterica*. Trophozoites (1 and 2), and cysts (3 and 4).

was renamed *Giardia intestinalis*. It was later pointed out that the specific name *intestinalis* was already occupied and that the correct name is *Giardia enterica*. The name *Giardia lamblia* is also used, but is not in accordance with the rules of nomenclature.

Epidemiology.—Giardiasis occurs in all countries, but is probably more common in the tropics. It is found in persons of all ages, but it produces more definite symptoms in children than in adults. It was found in 6.27 per cent of about 20,000 stool samples from a mixed population examined in Calcutta between 1935 and 1938. In children, the general infection rate is higher.

There appears to be no reason for attributing any racial predilection to this infection, and, although the incidence is to some extent inversely correlated with the sanitary sense of the community, it is not uncommon amongst classes that are very careful about their food and personal habits. There is little reason for believing that individuals of the classes that show the highest infection rate have acquired any tolerance to the ill-effects of the infection; the writer has frequently seen symptomatic giardiasis in such persons.

Ætiology and pathology.—*Giardia enterica* is a flagellate parasite with a trophozoite and a cystic stage. The former is pear-shaped and dorsally convex; it has a 'sucking disc' in its ventral concavity, and four pairs of flagella; it has a colourless granular cytoplasm, and two nuclei (not seen in the unstained specimen); in size it varies from 10 to 20 μ in length and from 5 to 15 μ in breadth; it is actively motile in the freshly-passed fluid stool, but soon loses its flagella and motility in a formed or stale stool. The cysts are oval, 8 to 12 μ in length and 7 to 10 μ in breadth; they are colourless, and have four nuclei and a well-defined cyst wall.

The parasite lives and multiplies in the intestinal tract, from the duodenum to the cæcum. Both the cysts and the trophozoites are found in the stools, but the trophozoites will be found in larger numbers in samples obtained by duodenal aspiration.

The flagellates become attached to the intestinal mucosa which they irritate, causing it to secrete an excess of mucus. It is also very probable that they affect the function of the mucous membrane and interfere with absorption. A variety of lesions has been attributed to giardia infestation, but it seems very doubtful if the parasite can be held solely responsible for any of them. It does not appear to have any invasive properties.

Symptomatology.—At present the symptomatology is not well defined, as the infection is so frequently associated with other infections, but a large variety of symptoms clear up when the infection disappears under specific treatment, and one is naturally inclined to attribute these to giardiasis. However, it is quite obvious that there are many persons with giardia infection, who suffer no recognizable ill-effects.

The most constant symptoms are: (a) diarrhoea—the stools are usually loose and watery, but may be definitely fatty; (b) abdominal pain or discomfort, either in the upper segment often associated with flatulence and sometimes with vomiting, and usually accompanied by loss of appetite; or in the lower segment, with griping pains usually relieved by defæcation; and (c) irregular fever.

Children also are usually irritable and tiresome, and develop capricious appetites. A condition very like celiac disease is recognized as being caused by giardiasis, and several of the writer's adult patients have shown a condition suggestive of sprue (*q.v.*) with marked anorexia, a sore tongue, macrocytic anæmia, and a fatty diarrhoea with actual increase of total fat in the stools. Specific treatment has caused a rapid disappearance of all the signs and symptoms.

In addition, adult patients often feel definitely ill and weak, and they may exhibit nervous symptoms, such as irritability and anxiety.

Abdominal tenderness is constant in the cases with symptoms; this is usually in the epigastrium, but sometimes in the region of the cæcum where some thickening of the gut can be felt in thin individuals.

Diagnosis.—The symptoms are too pleomorphic and too vague to allow an unsupported clinical diagnosis. The finding of the flagellate or its cysts in the stool is of course diagnostic of giardiasis, though the symptoms may be due to another cause, but flagellates are not always found, and duodenal aspiration may be advisable in a case under strong suspicion. This procedure is essential, if cure is to be definitely confirmed.

Treatment.—Of the innumerable treatments advocated, none proved really successful, until Brumpt (1937) and Martin (1937) introduced mepacrine (atebrin), which appears to be a specific.

A large percentage of complete cures will be achieved with a course of 0.1 gramme three times a day for five days. Children should be given smaller doses (*see* p. 101). A second course after an interval of about a week will be necessary in a few cases. If there is any doubt about the cure, it is advisable to give this second course.

CILIATE DYSENTERY : BALANTIDIASIS

Although balantidiasis is a rare infection, there seems no possible question that it occurs and may be serious. Some 250 cases have been recorded.

Geographical distribution.—Balantidiasis appears to have a universal distribution, but far more cases have been reported in temperate countries than in the tropics. Cases have been reported from most European and Asiatic countries, including both England and India, but it is not common in either; in the case of the latter, this will easily be understood. Two cases have been reported from North America, and several from South America and Africa.

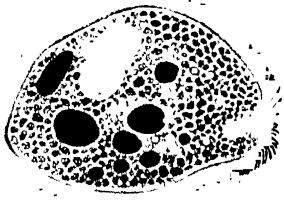


Figure 137 : *Balantidium coli*.

Occupational incidence.—It occurs in swine-herds and pork-butchers, and other persons closely associated with pigs.

Ætiology.—*Balantidium coli* is a ciliate protozoa, a natural parasite of pigs, to which it appears to do little harm. It is transmitted to man apparently by food contamination. Experimentally, it is transmitted with great difficulty.

Pathology.—The parasites invade the mucosa of the large intestine apparently in exactly the same way as does *Entamoeba histolytica*. The ileum has also been involved. Entering the crypts of Lieberkühn, the parasites secrete a kind of cytotoxin, and penetrate into the submucosa, and thence even into the intestinal lymph nodes. The ulceration produced is similar to that of amœbic dysentery. Perforation has been reported.

Symptomatology.—This is again indistinguishable from that of amœbic dysentery. The onset is often very insidious, but the condition may develop seriously, and it is usually very persistent. Anæmia is a marked feature, and later cachexia develops.

Diagnosis will be made only by finding the *Balantidium coli* in the stool. It is a large parasite easily seen with the low-power lens.

Treatment.—This has not been very satisfactory. Large (dangerous) doses of emetine, gr. 1 daily for 15 to 20 days, have produced a cure in a number of cases, and recently methylene blue—administered by mouth in

2-grain pills and as an enema in a strength of 1 in 3,000—has been used with some success. Drachm doses of carbon tetrachloride have also been used successfully.

Prognosis.—A number of deaths have been reported. The mortality can be placed at between 10 and 20 per cent.

In some cases, the infection has persisted for from four to fifteen years.

COCCIDIOSIS

Infections with the coccidium, *Isospora hominis*, are not rare in the tropics and sub-tropics, and are usually associated with sub-acute dysenteric symptoms.

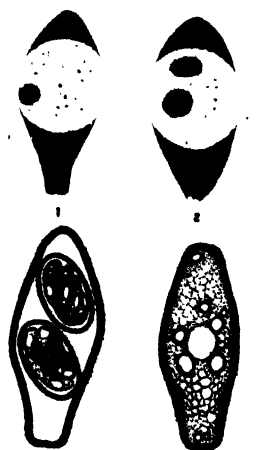


Figure 138 : *Isospora hominis*.

(Dobell and O'Connor, 1921.)

1. Oöcyst with unsegmented protoplasm, as usually passed in stools.
2. Later stage; nucleus divided into two.
3. Fully developed oöcyst, containing two spores—each containing four sporozoites.
4. Degenerate oöcysts, which have failed to develop.

Epidemiology.—The infection has been reported in most countries in the tropics and sub-tropics, but rarely in the temperate zones. The apparently greater frequency in the Mediterranean area probably reflects only the fact that greater attention has been paid to it there. In routine stool examinations in India; it is not such a rare finding that observers think it necessary to report each case: nine cases have been encountered in the last twenty years at the Calcutta School of Tropical Medicine (Das Gupta, 1934).

The majority of the infections reported have apparently been in adults.

Ætiology and pathology.—The parasite, *Isospora hominis*, infests the small intestine and invades the mucosa. The oöcysts, which are found in the stools, have the general appearance of helminthic ova; they are oval, 25 to 32 μ in length and 12 to 16 μ in breadth; they are colourless, and consist of a distinct cyst wall, a clear cytoplasm, and a central sporoblast with contained spores; the sporoblast is more or less round and occupies the whole breadth of the parasite.

Infection of man takes place in the oöcyst stage by the oral route.

A heavy infection will cause a catarrhal condition of the mucosa rather than ulceration, and will interfere with its functions.

Symptomatology.—Symptomless infections are not uncommon. Infection is usually associated with mild chronic diarrhœal symptoms, some malaise and mental depression, loss of appetite and weight, and occasionally epigastric discomfort.

The stools are light-coloured, contain much undigested food, and show a tendency to be fatty.

Diagnosis can be made only by finding the oöcysts in the stools. The only other characteristic finding, which is almost constant, is Charcot-Leyden crystals.

Treatment.—No entirely satisfactory treatment has been evolved, but the condition is not usually very persistent. The administration of bismuth salicylate, gr. 30, thrice daily and of a two-per-cent sodium bicarbonate enema appears to have been one of the most successful procedures.

HELMINTHIC DIARRHÆAS AND DYSENTERIES

The most important of the helminths *vis-à-vis* dysentery are those of the genus *Bilharzia*, but these will be considered when the important

syndrome caused by these parasites is discussed. Diarrhoeal symptoms have been associated with two other trematodes, *Fasciolopsis buskii* and *Heterophyes heterophyes*, and two nematodes, *Æsophagostomum apiostomum* and *Strongyloides stercoralis*.

Trematode diarrhoea.—*Fasciolopsis buskii* develops in certain species of snail, and thence the cercariæ infect the water-chestnut and other aquatic plants which are eaten by man. The infection is common in China and the Far East generally; many infections have been reported in India (Assam). The parasites live in the small intestine, and usually give rise to no symptoms at all when they are present in small numbers, but heavy infections cause a catarrhal condition of the gut which leads to diarrhoea, pain in the abdomen, œdema and ascites, and a serious condition of ill-health, which develops gradually.

Most antihelminthic drugs will effect a cure, e.g. carbon tetrachloride or tetrachlorethylene given in doses of 3 or 4 c.cm. with the usual precautions.

Heterophyes heterophyes infests dogs, cats and other carnivores, and man. They similarly develop in snails; the cercariæ are ingested by fish, and man becomes infected by eating insufficiently cooked fish.

If present in the small intestine in large number, they also produce a catarrhal condition of the mucous membrane. The clinical picture is similar to that associated with *Fasciolopsis* infection.

In the treatment of this infection, most of the ordinary anthelmintics have been tried, usually with good effect.

Nematode diarrhoeas and dysenteries.—*Æsophagostomum apiostomum* is a common nematode in monkeys in West Africa, and it occurs also in Asia; it has not been reported in India. The larvæ are swallowed, and reach the cæcum where they bury themselves in the mucous membrane, and develop. The nodule thus formed bursts into the lumen of the cæcum, and the worm attaches itself to the mucous membrane. Secondary infection of the site of the burst nodule causes ulceration, and the worms themselves cause excessive secretion of mucus, so that the symptoms may be either those of dysentery, or simply diarrhoea.

Carbon tetrachloride is recommended as an efficient treatment, but probably other anthelmintics would prove as satisfactory.

Strongyloides stercoralis, to which further reference will be made, also causes a diarrhoea.

REFERENCES

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|-------------------------|----|---|
| BRUMPT, L. (1937) | .. | .. Traitement Expérimental de la Lamblia. <i>Compt. Rend. Soc. Biol.</i> , 124 , 1040. (Abstract— <i>Trop. Dis. Bull.</i> , 1938, 35 , 592.) |
| DAS GUPTA, B. M. (1934) | .. | .. Observations of a Case of Coccidial Infection in Man (<i>Isospora belli</i> Wenyon, 1923). <i>Indian Med. Gaz.</i> , 69 , 133. |
| MARTIN, P. (1937) | .. | .. Nouveau Traitement de la Lamblia par un Dérivé d'Acridine. <i>Rev. Méd. et Hyg. Trop.</i> , 29 , 33. (Abstract— <i>Trop. Dis. Bull.</i> , 1938, 35 , 591.) |

CHRONIC POST-DYSENTERIC ULCERATIVE COLITIS

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Discussion.—Ulcerative colitis is not an exclusively tropical condition, and, in fact, has received far more attention in cosmopolitan medical literature than in that section of medical literature that deals mainly with tropical diseases. There has been much inconclusive discussion on the ætiology of so-called 'idiopathic' ulcerative colitis; we are little concerned with this, for, whether or not bacillary dysentery is a common cause of the ulcerative colitis of temperate countries, certainly a chronic ulcerative colitis is not an uncommon sequel to both bacillary and amœbic dysentery in the tropics. This ulcerative condition is distinguished from chronic amœbic dysentery and chronic bacillary dysentery—if such a condition really exists—by the fact that the primary causal organism has disappeared, or at least is no longer responsible for the main ulcerative condition.

Ætiology.—As has been indicated above, the condition we are considering here is not *now* maintained by either *Entamœba histolytica*, or one of the recognized dysentery bacilli, and the finding of a small number of organisms of either of these genera in the stools does not necessarily indicate that the main pathological process is maintained by them. For example, in bacillary dysentery (*q.v.*) a carrier state occurs in which small retention cysts containing dysentery bacilli burst periodically into the lumen of the gut; this state of affairs may be co-existent with, but be entirely independent of, a chronic ulcerative condition of the bowel. Similarly, a 'carrier' type of amœbic infection may exist in one part of the gut, when elsewhere there is a non-specific ulceration.

The principal micro-organism that is now maintaining the pathological process will probably vary from case to case. Streptococci are usually recovered most readily from the ulcers; but there is still much work to be done on the identification and classification of the flora of these ulcers.

Cultures from the stools may be misleading, and the true culprit is likely to be identified only by taking swabs directly from the ulcers, after colonic lavage, with the aid of the sigmoidoscope. Bargen's diplococcus, which, it is claimed, is frequently present in the 'idiopathic' form, has seldom been identified in the tropics.

The main predisposing factor is of course the damage done to the gut mucous membrane and deeper structures during the primary (specific) ulceration. It is not difficult to understand how such large denuded areas fail to heal whilst in more or less continuous contact with the septic gut contents. However, as we know that healing does frequently occur, we must consider why it does not always do so.

The general health of the patient is an important factor; this will often be largely influenced by climatic conditions, associated infections, and, probably above all, his state of nutrition. This latter will often be low, even in the well-to-do patient, from long periods of restricted diet.

PATHOLOGY

The ulcers may be in any part of the colon, but are usually in the sigmoid or rectum. The cæcum is the next most common site. The ulcers are usually oval in shape, but may be serpiginous. The edge may have a clean-cut punched-out appearance, or it may be rounded, hard and fibrous; it very rarely, if ever, shows the irregular undermined edge of the extending ulcer. The mucous membrane in the areas between the ulcers is usually healthy.

The ulcers are frequently deep, and there is infiltration of the muscular coats, with interference of the normal muscular action, and thickening of the bowel that can be felt through the abdominal wall. Later, there may be fibrosis and contraction in the deep layers of the intestinal wall, and a whole length of gut may become a rigid tube with a narrow lumen. More superficial scarring may lead to the isolation of areas of mucous membrane, with polypoid formations.

Blood.—There is no characteristic blood picture. There are two influences, the tendency to microcytic anæmia as a result of repeated blood loss from the ulcers, which may become an important factor, and the tendency to a nutritional macrocytic anæmia, from mal-absorption and/or dietary restriction; patients often develop a para-sprue (*q.v.*) condition. However, in the uncomplicated ulcerative colitis, the hæmoglobin may be almost normal. There is often a slight leucocytosis.

SYMPTOMATOLOGY

Clinical history.—The condition may develop after a single attack of dysentery, but more frequently it is established after a series of attacks, most of which may have been relatively mild, and the usual history is that they were inadequately treated either because the patient did not attach sufficient importance to them, or because of the circumstances in which they occurred.

The onset may however be entirely spontaneous and without any previous history of bowel disorder.

Symptoms.—When the condition is fully established, the patient will complain of more or less continuous discomfort in the abdomen, which is less insistent after a period of rest and dietary restriction, and is increased

after dietary (or alcohol) indiscretions, exposure to climatic extremes, especially cold, and subjection to physical, or more rarely mental, strain. This discomfort is usually on the left side, over the descending and sigmoid colon, but it may be over the cæcum or at the flexures. The pain may be partly relieved by defæcation or passage of flatus, but it rapidly returns. It is more noticeable shortly after food is taken.

The patient is always in a state of sub-health, and is easily tired; during exacerbation he feels definitely ill. He is often slightly anæmic, has an unhealthy 'muddy' complexion, and his skin is inelastic. He is often considerably emaciated, with a thin abdominal wall, through which the thickened bowel can be felt easily. There are points in the abdomen which are constantly tender.

A low pyrexia is common; this will amount to definite fever now and then, but usually the evening temperature is between 99° and 100°F.

The number of stools varies, but, except during the occasional periods of constipation, they are seldom less than three, or more than five or six; they are watery or soft and 'porridgy', but very seldom formed. They may show blood, and usually there is mucus or pus. After a period of constipation, there is usually much blood-stained mucus in the outside of the formed or semi-formed stool.

A very large number of secondary symptoms of an allergic, a toxic, and a neurasthenic nature are attributed to chronic bowel ulceration, and there is undoubtedly a causal relationship between many of these and ulcerative colitis. Patients with this condition are very liable to be hyperchondriacal, and to concentrate entirely on their bowel condition, often adopting a very unsuitable dietary regime of their own invention.

Diagnosis.—It is usually possible to make a provisional clinical diagnosis from the history and examination of the patient, which are frequently very typical.

The stools will often contain blood, mucus and pus, and under the microscope they will show a cellular exudate and red cells.

Sigmoidoscopic examination is, however, almost essential for satisfactory confirmation of the diagnosis. Typical ulcers will be seen in a relatively healthy mucous membrane; some of these will probably be healed, others breaking down. They usually bleed readily.

The **opaque enema** (by the use of thin well-diluted barium, administered slowly under low pressure into the previously prepared bowel) shows diminution or loss of haustration of the colon; at a later stage, the colon develops a smooth outline like that of a bicycle tube. There may be local areas of narrowing. Remnants of barium may be visible in the deeper ulcers after its evacuation. X-ray examination also shows the extent of the bowel involvement, and whether it is generalized or segmental.

TREATMENT

Once the diagnosis has been made, the patient should be made to realize that the treatment is bound to be very prolonged, and needs his (or her) full co-operation and patience.

He should rest in bed as long as there is fever or dysenteric symptoms. Later, he may be allowed a little licence, for example, to bathe himself and to sit in a long chair.

Preliminary administration of a sodium sulphate mixture, 2 dr., four-hourly from 6 a.m. to 6 p.m. for a few days will usually help to clear the large bowel of mucus and debris. It also frequently brings down the temperature. During this period, the diet should be restricted to fluids, e.g. milk, which may be citrated or peptonized, butter, milk, chicken broth, and fruit juice. Sometimes, considerable improvement can be effected by

giving by mouth some of the recognized arsenic or iodine preparations used in the treatment of amœbic dysentery (*q.v.*), and recently we have had several cases that have responded to sulphapyridine, this drug possibly knocking out the secondary streptococcal infection, but we have had many more failures than successes with it. However, no reliance can be placed in oral medication, and bowel washes are usually necessary.

Colonic irrigation.—Many drugs have been recommended, eusol, chiniophon, vioform, sodium sulphapyridine, and several organic silver preparations, but the writer has found silver nitrate as satisfactory as any of these more expensive drugs.

The medicated enema must be preceded by a sodium-bicarbonate bowel wash. A pint of warm two-per-cent bicarbonate solution is run in slowly, and the patient told to retain it for a few minutes; he is then encouraged to evacuate this completely. The medicated enema is then given; six ounces should be given at first, but later the amount is increased up to half-a-pint, if the distal portion of the colon only is affected, and, if the higher portions of the bowel are to be reached, the amount must be slowly increased up to a pint, and the patient placed for a short time in the knee-elbow position in order to help the fluid to reach the proximal portions of the colon. The bowel washes should be run in through a soft catheter, under low pressure (18 inches to two feet of water).

The strength of the silver nitrate solution should be 1 in 1,000 at first, and it should be slowly increased by stages to 1 in 750, 1 in 500, 1 in 400, 1 in 300, and eventually 1 in 250. If on any particular day the enema is very painful, it should be washed out with normal saline.

The patient should be encouraged to retain the medicated enema as long as possible, up to five hours. These washes should be given daily, or, if they appear to exhaust the patient too much, on alternate days, for several weeks, until all the symptoms have subsided and the returning fluid is entirely free from pus and red cells.

Diet.—This is a matter of the greatest importance. After the first few days of treatment, during which the diet should be mainly fluid, as suggested above, the patient must be got on to a high-calorie, well-balanced, residue-free diet, by rapid stages. The diet must contain adequate protein in some easily digestible form, and all the vitamins and minerals, but it must include only the minimum of residue. Plenty of fluid and adequate salt must be taken. A suitable diet has been suggested above (*see p. 420*).

General and symptomatic treatment.—The bowels must be kept regular by means of ispaghula, or some similar substance. Purgatives should if possible be avoided, but if they are necessary, only the mildest vegetable laxatives should be taken.

The anæmia should be treated with suitable hæmatinics as indicated by the blood counts, but very often it will be advisable to give both liver and iron. In severe cases, a blood transfusion will often initiate a period of improvement. Sedatives, analgesics, and antispasmodics may be required; it may be advisable to give a bromide mixture for a week or so at the outset, and at night, in order to ensure a good night's rest, codeine, or opium, the latter in the form of Dover's powder combined with bismuth salicylate.

Progress.—Except in the worst cases, all the symptoms will rapidly subside, the general appearance of the patient will improve, and he will put on weight. If the ulcers are at the lower end of the colon, the progress can be watched by means of the sigmoidoscope.

The principal danger will come from stopping both active and dietetic treatment too soon; even after an apparent complete cure, a relapse is very liable to occur unless great care is taken, regarding the diet in particular, for months or even years.

On the other hand, if the patient does not improve after two or three months' treatment, and after several changes of bowel wash, surgical treatment will have to be considered. Two operations are recommended, appendicostomy and ileostomy; by the former, a means of giving efficient bowel washes is provided, and by the latter the faecal matter from the upper bowel is side-tracked as well. The latter is undoubtedly more efficient, but the former is simpler to do, and much simpler to undo when it is no longer required. Care should be taken not to resort to surgery too late, because once the large intestine has become fibrotic, it will contract with disuse, and become a hard narrow tube that will never function again properly, and a permanent colostomy will be the result.

Prognosis.—This will depend on how early the treatment is undertaken, and on the vigour and skill with which it is prosecuted; this in turn will depend on the co-operation of the patient, and on the circumstances in which he is placed.

If proper treatment is undertaken early, cure should always be possible, but many neglected patients have passed into a stage of chronic invalidism, while other have gone rapidly down hill, and have died of exhaustion or intercurrent disease within a few months.

SPRUE

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Introduction.—Most of the early writers on sprue emphasized the fact that the disease was confined to Europeans or persons of mixed European and Asiatic descent. It has long been recognized that the incidence in different racial groups is in inverse ratio to the degree of pigmentation of their skins. There is, however, a natural tendency to report the rare case, so that the exceptional cases of sprue in Indians or other indigenous inhabitants of the tropics have received greater publicity than the ordinary run of cases in Europeans, with the natural consequence that the undoubted racial predisposition to this disease is not receiving sufficient emphasis in current medical literature. The writer has not yet seen a typical case of sprue in an Indian, though he believes that typical cases do occur amongst the fairer, northern Indians.

There occurs, however, commonly amongst Indians a now-well-recognized syndrome of macrocytic anæmia, nutritional in origin, that is often associated with a chronic watery diarrhœa. In some of these cases, there are certain signs and symptoms that are also typical features of the sprue syndrome, for example, emaciation and a sore, red and glazed tongue. In fact many of these cases in Indians would pass as modified sprue, and are often diagnosed as such.

There is also a condition of chronic watery diarrhœa, with perhaps a slightly sore tongue but at first without macrocytic anæmia, that occurs amongst both Europeans and Indians and is usually referred to as 'pre-sprue'. The name is not a good one, as, even if one does not take the view that true sprue never occurs in Indians, the name implies that sprue must inevitably follow unless the condition is cured. This is not the case, for, although many patients with sprue give a history of previous diarrhœa, this diarrhœal condition referred to here may continue for many months and even years without the patient's developing further typical symptoms of sprue; but emaciation, a sore tongue and a macrocytic anæmia are common sequelæ, so that the condition develops into the malnutritional syndrome described above as commonly occurring in Indians. For this condition the writer has for some years used the word 'para-sprue'.

While there are undoubtedly all degrees of conditions between (a) nutritional macrocytic anæmia, with or without diarrhœa, (b) para-sprue, and (c) true sprue, the writer believes that they are not just stages of the same condition, but that para-sprue and sprue have different ætiologies, just as they have distinguishable clinical pictures. The conditions are therefore described separately.

Definition.—Sprue, or psilosis, is a diarrhœal condition of uncertain ætiology, characterized by emaciation, the passage of large, light-coloured and frothy stools with a high fat content, flatulent dyspepsia, a sore tongue, a low glucose-tolerance curve, and eventually a marked macrocytic anæmia, occurring amongst people who live, or have lived, in certain tropical countries.

Historical.—Early historical records of this still not very clear-cut syndrome are not very clear, and it is obvious that many that are quoted might equally well refer to other diarrhœal diseases. Manson-Bahr (1939) considers that the descriptions of Ketelaer in 1669 and of Hillary in 1766 undoubtedly refer to sprue. The name was first used in the descriptions of Manson in Amoy and van der Burg in Java, in 1879 and 1880, respectively.

Recent contributions to our knowledge of this disease have been more destructive than constructive; for example, Thaysen (1931) and later Mackie and Fairley (1934) showed that our previous conception of the morbid anatomy of the disease was entirely erroneous.

EPIDEMIOLOGY

Geographical distribution.—'Sprue' without any qualification usually means 'tropical sprue', but there is little question that there is an indis-

tinguishable condition which occurs amongst persons who have lived all their lives in a temperate climate; to this the name 'non-tropical sprue' is usually given. Some 170 cases of non-tropical sprue have been described; these reports have come from several countries, mainly the U.S.A. and Great Britain.

Tropical sprue is most commonly associated with residence in China, India, Ceylon, Malaya, the East and West Indies, southern U.S.A., Central and South America, southern Italy, and Queensland; that is to say, it is for the most part truly tropical, but a few sub-tropical areas are included, and the disease is rare in tropical Africa. Its realm lies between 40°N. and 20°S.

Age and sex.—It is more common in females than males, and is essentially a disease of middle age, but it may occur in young people and even in children.

Race.—The negative correlation between skin pigmentation and sprue has been mentioned above. The disease is commonest amongst European and fair Eurasians; it is uncommon amongst Chinese, Malays, and fair northern Indians; it is very rare in dark southern and eastern Indians; and it is apparently unknown in negroes.

Climate and locality.—It occurs mainly but not entirely in hot, damp, coastal climates. Instances have been reported of residents in desert areas getting the disease, and a number of cases have occurred amongst sailors who have spent little time ashore.

It is regional as well as climatic; that is to say, sprue is often common in one and rare in another of two places that appear to be climatically identical. It often follows long or frequent hill residence and repeated attacks of hill diarrhoea.

Seasonal.—The onset is usually after or during the rains.

Other epidemiological observations.—Sprue houses, in which a succession of residents have suffered from sprue, have been reported, and this has led to theories regarding its infectious nature; also, husband and wife not infrequently both suffer from the disease. It has been specifically associated with heavy white-ant infestation of the house, and with dry rot, neither being very unusual associations in the tropics.

Time relation to tropical residence.—It is usually associated with long tropical residence, and it is common in the domiciled European in tropical countries. Many cases have been reported amongst retired tropical sojourners, several years after they have returned to a temperate climate; this has been referred to as *latent sprue*. On the other hand, it is by no means uncommon for sprue to develop after a very short residence.

ÆTIOLOGY

. There are numerous theories regarding the ætiology of this disease :—

(a) **The infection theory.**—There are still a large number of writers who believe that the evidence is in favour of some infective organism being the cause of the disease. This school is at present represented by Manson-Bahr (*loc. cit.*) who gives the following reasons for his belief :—

- (i) Sprue has a definite incubation period, of usually three to six months after residence in the tropics.
- (ii) The geographical distribution is patchy and peculiar.
- (iii) Evidence has been collected that several members of the same family living under the same conditions may contract the disease.
- (iv) Clinical observations suggest that sprue is a specific inflammation ranging through the intestinal tract and affecting principally the process of assimilation, and that it is brought about by some specific virus affecting the mucous membranes. It may be assumed that this virus is capable of lying dormant in the tissues for a number of years and may then be roused into activity by some unknown factor.

There are certain points in the epidemiology of this disease which are hard to explain except on the infection theory, but the two main criticisms of the above-quoted points are that the incubation period of sprue is far from constant, and that all recent pathological evidence is against there being a specific, or in fact any other, inflammatory condition of the whole intestinal tract.

The organisms under suspicion can be grouped as follows :—

(i) *Monilia*. *Monilia psilosis*, or *Parasaccharomyces ashfordi*, has been the organism mainly suspected. This theory was supported by Kohlbrügge, Ashford (1929), and Manson-Bahr, but it is now generally considered that their presence is simply a matter of the suitability of the bowel contents in sprue as a medium for these organisms. It has been shown that this and other moniliæ are present in the bowel under normal conditions, and that in any diarrhoeal condition they may become more abundant (Mackie and Chitre, 1928, and Pasricha and Lal, 1939).

(ii) *Streptococcal infections*. Rogers was one of the earliest exponents of this theory. Hæmolytic streptococci are usually obtainable from the stool and mouth, but are probably secondary invaders.

(iii) *Some other specific organism* as yet unidentified, possibly a virus.

(b) **Calcium deficiency**.—The total calcium is below normal in about half the cases, but the more marked deviation from normal is the reduction in ionic calcium, which was at one time thought to be due to dysfunction of the parathyroid, possibly caused by excessive strain on its detoxicating functional activity.

It is obvious that this low calcium content of the blood, which is shown clinically by tetany, a not uncommon symptom, is only a small part of the general picture, and is almost certainly due to failure of calcium absorption, since calcium forms an insoluble compound with the soaps in the intestinal canal, and possibly to some extent to failure of calcium metabolism, resulting from the general endocrine imbalance.

(c) **Simple failure of absorption**, due to degenerative and atrophic changes in the intestinal mucosa. Recent work has shown that there are no constant histological changes in the mucosa of the gut in sprue.

(d) **Food deficiency**.—Cantlie (1913), Elders (1919) and McCarrison (1919) amongst others suggested that it was a food deficiency, vitamin A and B-complex and certain specific amino-acids being specially selected, and Castle and Rhoads (1932) considered that it was due to the absence of the extrinsic hæmopoietic factor in the diet or of the intrinsic factor in the gastric secretion, or to the failure of absorption of the combination of these factors by the intestinal mucosa.

Against this simple food-deficiency theory is the fact that many persons who have lived on an excellent and well-balanced diet have developed sprue, that the diet of persons of the class in which sprue most commonly occurs is not on the whole particularly deficient, and that, though sprue may be associated with other deficiency conditions, there are many population groups on notoriously poor diets whose individual members suffer from various deficiency diseases but these seldom include sprue.

(e) **Metabolic failure**.—Finally, Fairley has suggested that it is a metabolic failure, a functional rather than a mechanical failure to absorb and to utilize both fats and carbohydrates.

* Recently this theory has been developed and elaborated. Two important papers on this subject, by Hurst (1942) and Leitner (1942), have been published. The former has given an excellent review of the subject; he emphasizes the important known facts regarding the ætiology of the disease, and has suggested that the main failure is in paralysis of Meissner's plexus which controls the muscularis mucosæ, with subsequent

Physiology of intestinal fat absorption.—Neutral fat in the small intestine is split by the pancreatic lipase in the presence of bile. After absorption by the epithelium of the villi, the fatty acid combines with glycerol to be later resynthesized into neutral fat. An intermediate process, known as phosphorylation, which accelerates absorption of not only fats but also of carbohydrates and other substances, takes place in the epithelium of the villi. After absorption and resynthesis, the fat goes to the central lacteal of the villus, whence it is pumped by the rhythmical contractions of the muscularis mucosae into the main lacteals. The pumping action is controlled by Meissner's (submucous) plexus, which in turn is, it is believed, controlled by an intestinal hormone (villikinine) which is extracted from the intestinal mucosa by hydrochloric acid.

The contractions of the villi and the whole process of absorption are subject to the influence of the endogenous adrenal cortical hormone and also of yeast extract, presumably vitamin-B complex—though many individual elements of this complex do not alone influence absorption—in the food; the hormone and the vitamin-B complex act to some extent reciprocally.

Discussion.—The writer believes that there is considerable evidence that sprue is caused by an inborn error of metabolism which normally remains latent but becomes patent when the organism is subjected to certain strains and stresses, especially those associated with tropical residence.

The nature of the disease is far more that of a metabolic disorder than of an infection; it is peculiar to certain racial types, and, once the defect is unmasked, it shows a marked tendency to relapse, and permanent recovery without change of habits and/or environment is unusual.

This 'error' leads primarily to a failure of absorption in the small intestine, of fats, vitamins and minerals, and to a less extent of carbohydrates; the fatty and fermenting stools and the emaciation are due to failure of absorption of fat and carbohydrate, but all other symptoms are due to vitamin and mineral deficiencies, as a direct result of malabsorption or deflection, of these elements. The syndrome of tropical sprue is probably identical with that of coeliac disease, except that the latter becomes patent earlier in life and is not necessarily associated with tropical residence, and with that of non-tropical sprue, which, though the evidence of the 'error' appears in later life, does not need the excessive strain of tropical conditions to bring it to the surface. The degree of the error is thus greatest in coeliac disease, less in non-tropical sprue, and least in tropical sprue; the response to treatment is in the reverse order.

Sprue is similar to pernicious anæmia mainly in that the latter is also an inborn error which only becomes apparent in later life, but a very different portion of the intestinal tract is affected. The symptoms common to these two conditions are due to 'hæmopoietin' deficiency, in pernicious anæmia on account of the absence of intrinsic factor, and in sprue on account of failure of absorption of the combined intrinsic and extrinsic factors, or to deflection of the latter.

In sprue, there are often pellagra-like symptoms. The most important cause of pellagra is niacin (nicotinic acid) deficiency; this may be due to an actual deficiency of niacin in the food, to its neutralization or deflection by porphyrins, or to a failure of absorption through some intestinal defect. This intestinal defect in pellagra may also be of a metabolic nature and/or caused by endocrine imbalance; for example, the writer recently had a persistently relapsing case of pellagra in which there was thyroid deficiency, and in which the pellagra was cured by thyroid extract without the addition

failure of the pumping action of the villi. The latter's paper is also full of suggestive observations, but his conclusions fail to carry conviction because they appear to depend largely on the assumption that achlorhydria is a constant—or at least a very common—finding in sprue; in ours and other's experience, some hydrochloric acid is secreted in about three-quarters of the cases of sprue. In pellagra, however, we have found almost constant achlorhydria.

of niacin. The pellagra-like symptoms of sprue are due to failure of absorption of the vitamin-B₃ complex which includes niacin.

The populations that suffer from pellagra seldom suffer from true sprue, and, though the two diseases are sometimes associated in the same person, they are nevertheless two distinct diseases, and probably have totally different ætiologies.

The association with dysentery (even if it bears statistical examination which seems probable, though it must be remembered that dysentery is a very common tropical disease) may be a partial correlation due to the fact that a low gastric acidity, which is part of the sprue syndrome, predisposes to bowel infections. Further, dysentery is probably an important precipitating factor, in that it interferes mechanically with nutrition, especially in the acute bacillary form in which very rapid passage through the small intestine is the rule.

Vedder (1940) has suggested that the error may be associated with the anterior pituitary. It is not very clear exactly why Vedder has suggested the anterior pituitary, except that it is a 'master gland' and controls the function of several other glands, especially the thyroid and adrenals, and, in our present state of knowledge, the writer feels that it would be better to postulate endocrine imbalance rather than any specific dysfunction.

What remain to be discussed are the **precipitating factors** associated with tropical residence; these probably include a hot damp climate in which there is nearly always hyperæmia of the skin with relative visceral ischæmia, a monotonous ill-balanced diet rich in carbohydrates and poor in good protein, vitamins, and minerals, and debilitating infections, particularly malaria and those associated with the gastro-intestinal tract.

PATHOLOGY

Morbid anatomy.—The heart is small and shows brown atrophy. The liver, spleen, and kidneys are small, a 20 to 30 per cent decrease in weight sometimes being found.

There are no specific histological changes in any part of the gastro-intestinal tract. In the duodenum and jejunum, there is flattening of the valvulæ conniventes, and general thinning of the mucous membrane, sub-mucosa and muscular coats, through wasting of the last-named, and dilatation of the gut.

The desquamation that has been described is almost certainly a post-mortem change, and any ulceration is only incidental and not a part of the specific pathological picture. The mucous membrane is, however, usually coated with viscid mucus.

There is atrophy of the mucosa of the tongue, often associated with, and disguised by œdema, loss of sub-mucous tissue, thinning of the mucous membrane and flattening or loss of the papillæ. The mucous membrane is thus easily damaged, with resultant general soreness and aphthous ulcers.

The **bone-marrow** may show a megaloblastic hyperplasia, but this is not a constant finding and will seldom be found in those cases in which the anæmia is normocytic; at post mortem, the marrow shows, in addition to the usual hyperplasia, a gelatinous appearance, which is often found in malnutritional conditions and is probably due to specific starvation.

Suprarenal atrophy and degenerative changes in the **pancreas** are also described.

Blood.—There is a decrease in fat to 0.4 g. (normal = 0.6 g.) per 100 c.cm., and in the calcium which is usually about 7 to 9 mg. Cholesterol is often reduced to 70 mg.

The blood glucose curve, after 50 grammes of glucose by mouth, normally rises to 30 to 50 milligrammes per 100 c.cm. above the fasting

level at the end of one hour; 30 milligrammes may be looked upon as the low limit of normality. In sprue, the rise is usually less than 30 mg., and in an appreciable percentage of cases is less than 10 mg.

On the other hand, after intravenous glucose (50 grammes), the curve rises to 400 mg. or so, and remains high for much longer than in the normal person. This indicates a poor absorption of carbohydrates and a hypoinulinæmia, probably as a result of carbohydrate starvation.

The van den Bergh (indirect) reaction is usually slightly above normal, and the urobilin in the urine is increased.

Quite a marked degree of anæmia is the rule, most well-developed cases showing less than 3,000,000 red cells per c.mm. While, in a typical case, a macrocytic anæmia is found, this is not constant; only 61 per cent of Manson-Bahr's series had a colour index above 1. However, a true microcytic anæmia is uncommon, and when it occurs it must be attributable to some exceptional secondary cause (*i.e.* it cannot be accounted for simply by the failure of iron absorption).

There is seldom a high megaloblast percentage in the sternum puncture.

Gastric analysis.—Free acid is usually present, but the acid curve is low. Fairley (1930) found achlorhydria in 14 of 44 cases. Hanes (1942) found only 21 per cent histamine-fast achlorhydria; we have found a similar percentage.

Stools.—The first stool in the morning is nearly always bulky, pale and frothy; for the rest of the day, the stools are pale and fluid, but occasionally normal in appearance. The white appearance is not due to absence of urobilinogen, but to its conversion into leucobilin by the action of intestinal bacteria.

Normally, the total fat is 10 to 25 per cent of the weight of the dry stool; of this two-thirds is split fat. This split fat is found in the stool as fatty acid or combined as soapy fat. One-third remains as neutral fat.

In sprue, in 80 per cent of cases the fat is over 25 per cent and it may be 60 per cent*; two-thirds of this is split, but even more may be split, so that neutral fat to split fat may be 1 to 3 or even 5. The fat content of the stool is to a large extent dependent on the fat content of the diet, so that a standard diet should be consumed for several days before the test; a diet containing not more than 100 grammes of fat should be aimed at.

The important point is that, though the pancreas is doing its work, the fat is not being absorbed and utilized.

* **Estimation of fat in stools.**—There is no bedside method for the differential estimation of the fat content of a stool. This is necessary if the diagnosis between sprue and pancreatic disease has to be made, but in most circumstances the estimation of the total fat will give all the information necessary. The following method advocated by Hanes (1942) is relatively simple and apparently accurate.

Method.—The stool sample is mixed very thoroughly with distilled water to the consistency of thick soup; it is then strained through a fine sieve; it is again mixed thoroughly; and two portions are taken. (1) One is weighed, dried and again weighed, and the percentage of solids thus ascertained; (2) the other is weighed and the total fat in it is extracted and weighed; and (3) from these two figures the proportion of total fat to total solids is calculated.

Reagents.—9N sulphuric acid (approximately); 95 per cent ethyl alcohol; ethyl ether, *B.P.*; petroleum ether, *B.P.*

Technique.—(1) On an analytical balance weigh to milligrammes a 5 to 10 g. sample in a tared 50 c.cm. pyrex beaker. Dry in an oven at approximately 115°C. for about three hours. This will give the dry weight of stool, and can be carried on during the fat extraction, which is carried out on another sample as follows:—

(2) At the same time, weigh out to milligrammes a 3 to 5 g. sample of the watery well-mixed stool directly into the bottom of a 50 c.cm. round-bottom narrow-neck centrifuge tube, taking care to keep material from the sides of tube. Add 1 c.cm. of 9N sulphuric acid and make to approximately 5 c.cm. with water. Add to this

SYMPTOMATOLOGY

Patients often give a history of an attack of dysentery which is followed by troublesome diarrhoea, for which they have received a variety of treatments with correspondingly varied results. Amongst these treatments is always included a long period of restricted dietary. On the other hand, the onset is quite frequently unassociated with previous bowel trouble.

The onset may be slow and mild, mild but insidiously progressive, or rapid and severe.

Symptoms.—There is general lassitude and weakness, soreness of the mouth and dysphagia, particularly for hot food or spices, indigestion and meteorism but seldom vomiting. There is morning diarrhoea, large frothy and bulky stools constantly, with occasional attacks of loose stools throughout the day (but the stools after the first are often formed).

There is both mental and bodily irritability, and often neurasthenia; tetany, cramps, and muscular twitchings, and paræsthesias are not uncommon.

The appetite is usually poor, but occasionally the patient is ravenous, with disastrous results.

In the well-developed case, the patient has a sallow muddy complexion and a parchment-like skin with patchy pigmentation on different parts of the body, *e.g.* the malar eminences, forehead, buttocks, etc., the nails are brittle and the patient is emaciated and anæmic. The anæmia may be very prominent and many of the symptoms may be attributable to this. A low irregular fever is not uncommon, but is not part of the syndrome.

The tongue has a characteristic appearance; at first it is red and sore, the mucous membrane is thickened, œdematous, and folded, then later it is red and smooth with loss of papillæ; aphthous ulcers form on the frenum and edge of the tongue and in the mouth generally. If a piece of filter paper or handkerchief is applied to the tongue, normally it will leave a matt surface, but in sprue the tongue will remain shiny as if still wet.

There is the characteristic tumid lower segment of the abdomen, with the thin abdominal wall distended and drum-like. Peristaltic movements

an equal volume of 95 per cent ethyl alcohol. Heat in a boiling water-bath for two minutes. Cool thoroughly under running water. Add 15 c.cm. of ethyl ether, stopper with cork stopper, and shake vigorously. Add 15 c.cm. of petroleum ether, stopper, and shake vigorously. Centrifuge at low speed for three minutes. Transfer the clear supernatant fluid to a shallow-bottom, 50 c.cm., conical centrifuge tube. Evaporate the ether cautiously by heating the tube in a small beaker of hot water, taking precautions to prevent bumping. For this purpose a small special stirring rod, with a curved, beaded tip, is placed in the tube. Repeat the extraction of the alcoholic stool mixture 4 or 5 times, using 15 c.cm. portions of ethyl ether and petroleum ether each time as before, and evaporating the supernatant fluid cautiously after each extraction.

The residue from the extractions remaining in the conical centrifuge tube is dried by heating the tube in boiling water-bath for ten minutes, making sure that no alcohol, ether, or water remains in the tube. Cool and add 30 c.cm. of petroleum ether, washing down the stirring rod and the sides of tube, and stirring up the residue well. Centrifuge at low speed. Transfer the clear supernatant fluid to a tared 50 c.cm. Erlenmeyer flask. Evaporate the petroleum ether slowly by heating cautiously on a steam bath. Repeat this extraction with 30 c.cm. portions of petroleum ether four times, transferring the supernatant fluid to the 50 c.cm. Erlenmeyer flask, and evaporating off the petroleum ether each time. After the last evaporation no petroleum ether should remain.

Dry the flask on the outside and place this flask and the beaker from (1) containing the oven-dried sample of stool, in a vacuum desiccator for one hour. Weigh the beaker to milligrammes and the flask to tenths of milligrammes, using an analytical balance.

(3) Calculation :—

$$\frac{(\text{gm. of stool before drying}) \times (\text{gm. of fat in flask}) \times (100)}{(\text{gm. of dried stool}) \times (\text{gm. of stool taken for fat extraction})} = \text{per cent fat in dried stool.}$$

may be visible, there are borborygmi, and the liver dullness is diminished; this is due to an actual decrease and to the general distension of the intestines.

There is usually œdema of the legs, and often loss of knee jerks.

Röntgenological findings.—The normal feathery or herring-bone appearance of the upper part of the small intestine will be absent, and there are irregular local dilatations which suggest loss of tone; yet the bowel usually empties rapidly; the colon is reached in three hours, and the small intestine empties in six hours. The large intestine usually empties rapidly also, but there may be obstinate stasis here.

Progress.—The condition progresses steadily if rigorous treatment is not undertaken. With half-hearted treatment there may be periods of remission, but eventually symptoms will recur and the disease progress. Death is due to exhaustion and intercurrent disease.

The condition may improve and remain latent for some time, and then relapse after one or two years, but sometimes after a longer period.

DIAGNOSIS

There are naturally differences of opinion regarding the criteria for the diagnosis of sprue. The fully-developed case of sprue will exhibit the following characteristics :—

- (a) *Emaciation*, usually marked.
- (b) *A sore red tongue*.
- (c) *Characteristic stools*, usually bulky, frothy and white, but sometimes watery, containing total fat at least 30 per cent of the dry weight when the patient (adult) is fed on a diet containing not more than 100 grammes of fat per day.
- (d) *A low glucose-absorption curve*, not rising more than 30 mg. after 50 grammes (adult); or perhaps a more accurate measure is a rise of not above 40 mg. after 1 gramme per kilogramme body-weight (Hanes, 1942).
- (e) *Anæmia*, with cells rather larger than normal.
- (f) *Hypochlorhydria*, but not usually (20 per cent of cases only) histamine-fast achlorhydria.
- (g) *Röntgenological appearance*. Loss of the normal feathery or herring-bone appearance of the upper part of the small intestine.

While the above are the criteria for a well-developed case of sprue, the steatorrhœa must be looked upon as the only *sine qua non*, and there are many cases of undoubted sprue in which the syndrome is far from complete. On the other hand, of course, steatorrhœa is not necessarily diagnostic of sprue, as it occurs in many other conditions.

Differential diagnosis.—This subject can best be discussed under seven headings corresponding to the seven diagnostic points enumerated above :—

Emaciation.—There are many conditions, such as **malignant disease, tuberculosis, Addison's disease, anorexia nervosa, thyrotoxicosis and diabetes**, in which there will be wasting without any other obvious physical signs, but in none of these are the other diagnostic signs of sprue present.

Sore red tongue.—The tongue of sprue is not really different from that of **pellagra or pernicious anæmia**, nor in a mild case from that of the **Plummer-Vinson syndrome, nutritional macrocytic anæmia, or ariboflavinosis**.

There is much overlapping between the pellagra and the sprue syndrome, but there is seldom typical pellagra dermatitis in sprue, and never the steatorrhœa in uncomplicated pellagra and seldom the low glucose-absorption curve. Pernicious anæmia also is excluded by the absence of these two conditions, and, further, emaciation is unusual in the latter disease; in sprue the neurological symptoms are seldom marked, histamine-fast achlorhydria is not the rule, nor is the true megaloblastic picture, as reflected in the blood and bone marrow, ever present, and the van den Bergh indirect test usually gives a low reading.

In the Plummer-Vinson syndrome, the throat is usually affected, the anæmia is microcytic and, except the low gastric acidity, other typical symptoms of sprue are absent.

Some degree of ariboflavinosis is often present in sprue, on account of the poor absorption, and in nutritional macrocytic anæmia, the blood picture and gastric-acidity curve may also be very similar to that of sprue, but in both these conditions, if they are uncomplicated, the steatorrhœa will be absent and usually the emaciation.

Fatty stools.—(Cœliac disease and 'non-tropical' sprue are not included here as we consider them analogous to 'tropical' sprue, as has been indicated above.) In **pancreatitis** or **pancreatic tumour**, the unsplit fat is increased at the expense of the split fat, and there may be sugar in the urine.

In **abdominal tuberculosis** the fever and the abdominal condition should give some clear indication if the disease has reached the stage of steatorrhœa; also tubercle bacilli should be found in the stools.

In **giardiasis**, a heavy infection of giardia will be necessary to produce steatorrhœa and this will be identified easily; the diagnosis can be confirmed by the therapeutic test.

Low glucose-absorption curve.—This is not very uncommon in normal individuals, and may be very marked in **para-sprue** (*q.v.*). Though common in sprue it is not a very helpful differential diagnostic point.

Anæmia.—Pernicious anæmia, nutritional macrocytic anæmia and the Plummer-Vinson syndrome have been discussed above.

Hypochlorhydria.—As a rule, free acid is either low or absent. This condition is common to many other diseases; alone, therefore, the finding is of no positive diagnostic significance. On the other hand, in about 80 per cent of cases of sprue, pernicious anæmia will be excluded by the finding of some free acid.

Röntgenological appearance.—A similar appearance will be found in many cases of vitamin-B-complex deficiency (Mackie and Pound, 1935).

In addition to these conditions, **gastro- or duodeno-colic anastomosis** will produce a condition very similar to sprue.

TREATMENT

Introduction.—It has been said of sprue that there are 365 infallible cures. It is easy to understand the multiplicity of the specifics, since there are so many deficiencies that go to make up the sprue syndrome. The rectification of any one of these may go a long way towards restoring the general balance. Hence calcium, given in several forms, with and without parathyroid extract, niacin (or nicotinic acid), riboflavin, and liver extract have each been claimed as specifics and have undoubtedly effected cures in certain cases, but, without the dietary regime and rest in bed, patients exhibiting the full sprue syndrome will seldom be cured.

There is thus no short cut to treatment of this condition; patients must be warned that their whole-hearted co-operation is essential and that they must be prepared to face a period of at least two months of hospital, or the equivalent, treatment.

The treatment consists of rest in bed, a strict dietary regime, and treatment for the anæmia and gross deficiency conditions; otherwise, it is symptomatic. In the cases in which there is macrocytic anæmia, parenteral liver extract must be given in full doses, and, in view of the fact that many of the patients will have been living on a restricted diet, iron should also be given. Niacin may also be given with advantage in most cases, preferably by injection. The liver extract will usually produce an immediate

improvement in the blood picture, and also in the general condition, but even in the cases in which anæmia is the most prominent symptom, this treatment alone is seldom sufficient. Those reported cases in which liver treatment alone was effective were probably not true sprue but para-sprue or nutritional macrocytic anæmia.

Diets

Rationale.—The object of the dietary is to rest the disorganized fat and carbohydrate digestive mechanism, and at the same time to ensure proper nutrition to the tissues. This is best done by giving a high protein diet with a sufficiency of all the vitamins and essential minerals, and at the same time restricting the fat and carbohydrate intake.

If this principle is observed, the details are not of very great importance and the diet will certainly have to be varied according to the circumstances under which the patients are being treated, as well as from patient to patient.

The ratio of protein : fat : carbohydrate in a normal diet is 1 : 1 : 5. In a sprue diet, the proportions of fat and carbohydrate must each be reduced by at least two-thirds.

Milk diets.—One of the oldest forms of treatment was with milk. By using skimmed milk, it is possible to devise a milk diet that will very nearly meet the above requirements, or, if there is any difficulty about obtaining suitable milk, 'sprulac', a proprietary (Cow and Gate) preparation of dried milk with an exceptionally low fat content ($P = 1.0 : F = 0.3 : C = 1.3$), should be given.

The five stages of this milk diet are given in table VIII below. The feeds must be taken every two hours, from 6 in the morning until 8 at night, with an extra milk feed at 2 o'clock in the morning if the patient is awake; this makes 8 milk feeds and one fruit meal, the latter in the middle of the day. The milk must not be drunk from a cup, but sipped from a spoon, at least at first.

Some patients find it difficult to take fresh milk, but this difficulty is usually overcome by suitable treatment of the milk, *e.g.* by peptonization or citration, or by the occasional substitution of butter milk or some

TABLE VIII

Stages			1	2	3	4	5
Milk, skimmed : pints	3	4	5	5	4
" whole :	1	2
Fruit*, ounces	8	8	8	8	8
Glucose, ounces	1	1	1	1½	2
Eggs	1	2
Butter, ounces	½
Rusks*, ounces	1	2	3	3
Calories	846	1,166	1,480	1,986	2,412
Proportions							
Proteins	1	1	1	1	1
Fats	0.1	0.1	0.1	0.3	0.5
Carbohydrates	2.2	2.2	2.2	2.3	2.5

* See footnotes to table IX.

TABLE 1A

Showing the dietary items, their quantity, their protein (P), fat (F) and carbohydrate (C) content, and their calorie value, in the five stages of the sprue diet

Stages	I			II			III			IV			V		
	Oz.	P	F	C	Cal.	Oz.	P	F	C	Cal.	Oz.	P	F	C	Cal.
Article of food	48	48	5	67	505	60	60	6	84	630	40	40	4	56	420
Skimmed milk	20	20	2	28	210
Whole milk	20	36	44	56	764
Fruit* (orange juice)	8	2	..	22	96	8	2	..	22	96	8	2	..	22	96
Glucose	1	30	120	14	45	180	2	60	240
Chicken	208	4	34	8	..	208
Rusk†	110	1	2	2	21	110	2	4	4	42	220
Liver soup	69	8	24	2	6	138	8	24	2	6	138
Fish	4	22	5	..	133	8	44	10	..	266
Lean meat‡ (beef)	4	30	14	..	246
Egg (boiled)	1	3	3	..	43
Biscuit (plain mild)	1	3	5	8	264
Butter	4	..	12	..	108
Liver (lightly cooked)	4	24	3	3	135
Total	..	50	5	119	721.	..	110	17	160	1,233	..	168	69	235	2,237
Ratio P:F:C	..	1.0:0.1:2.3	1.0:0.2:1.4	1.0:0.2:1.2	1.0:0.4:1.4	..	1.0:0.5:1.4	..

A cup of weak tea with skimmed milk with glucose (or equivalent amount of sugar) from the ration can be taken once in the second and third, twice in the fourth, and three times in the fifth stages.

Notes. * *Fruit*. Orange, grape, and grape-fruit juice, and mashed bananas, papaya, bael fruit, and apple have been those most used by us, but some other fruits, e.g. strawberries, if and when they can be obtained, are suitable.

† *Rusks* are bread baked in an oven until crisp; one ounce of bread will make about 2½ ounce of rusk.

‡ *Meat* (beef or mutton) must be lean and raw; it should be cut into very thin slices and cooked for *not more than one minute* in a double saucepan, or in a thin frying-pan over a saucepan of boiling water. The meat becomes a light-brown colour, and loses its raw appearance and taste.

If the nurse is preparing the meal, it is only necessary for her to place the thin slices of raw meat (or liver) on the plate on which it is to be served and to place the plate over a saucepan of boiling water for about three minutes. The meat or liver can be cut up and eaten, or it can be minced; in the latter case, salt, pepper and marmite should be added, and, if a dry meal is preferred, about half an ounce of rusk crumbs (from the ration) should be mixed with the mince.

proprietary preparation, such as Benger's food; bovril added to milk will provide a change.

If sprulac is used, it must be given as follows :—

First stage, 6 ounces of sprulac (125 calories to the ounce of dry powder), to which water is added to bring the amount up to 48 ounces, that is, 1 part of dried milk in 8 parts of water; in the succeeding stages, 8, 10, 12 and 15 ounces of dried milk are given, with the fruit, glucose, etc.; in the fourth and fifth stages, respectively, a quarter and half ounce of butter are added.

Mixed diet.—In the tropics, a diet which is basically of milk, but to which other food substances are gradually added, will usually be found the most generally useful; the diet on these lines that we have used for several years is shown in table IX. At least eight 'meals' should be taken during the day, and the patient must be given an exact programme to follow.

Meat diet.—The high-protein diet recommended by Fairley consists largely of beef; good quality beef is difficult to obtain in many tropical countries, and, further, to many patients, beef is not only an unpleasant food, but does not seem to suit them even if they can be persuaded to take it. However, many patients come under treatment in a temperate climate and this diet has certainly been very successful in its originator's hands.

Fairley (1939) recommends the following diet :—

TABLE X

HIGH PROTEIN MEAT DIET

Diet No. 1 (calorie value = 770)

8 a.m.—Underdone beef, 3 oz.; rusks, $\frac{1}{2}$ oz.; juice of $\frac{1}{2}$ orange; and glucose, 2 drachms.

12 noon.—Soup, 4 oz. + liver extract (= $\frac{1}{2}$ lb.); underdone beef, 3 oz.; rusks, $\frac{1}{2}$ oz.; juice of $\frac{1}{2}$ orange; and glucose, 1 drachm.

6 p.m.—The same as at 12 noon.

Protein : fat : carbohydrate = 1.0 : 0.3 : 1.2.

Note.—When patients are very ill, two-hourly feeds of meat and beef-juice can be substituted.

Diet No. 2 (calorie value = 1,280)

8 a.m.—Underdone beef, 5 oz.; rusks, 1 oz.; calves-foot jelly, 2 oz.; juice of 1 orange + glucose, 2 drachms.

12 noon.—Soup, 4 oz. + liver extract (= $\frac{1}{2}$ lb.); underdone beef, 5 oz.; rusks, 1 oz.; juice of 1 orange + glucose, 2 drachms.

4 p.m.—Tea, 10 oz.; milk, 2 oz.

7 p.m.—The same as at 12 noon + calves-foot jelly, 2 oz.

Protein : fat : carbohydrate = 1.0 : 0.3 : 1.0.

Diet No. 3 (calorie value = 1,820)

6 a.m.—Tea, 10 oz.; milk, 2 oz.

8 a.m.—Underdone beef, 6 oz.; rusks, $1\frac{1}{2}$ oz.; calves-foot jelly, 2 oz.; juice of 1 orange + glucose, 2 drachms.

10 a.m.—1 baked apple; custard, 1 oz.

12 noon.—Soup, 4 oz. + liver extract (= $\frac{1}{2}$ lb.); underdone beef, 6 oz.; calves-foot jelly, 2 oz.; rusks, $1\frac{1}{2}$ oz.; juice of 1 orange + glucose, 2 drachms.

4 p.m.—Tea, 10 oz.; milk, 2 oz.; baked apple, 1 oz.; custard, 1 oz.

7 p.m.—The same as at 12 noon.

Protein : fat : carbohydrate = 1.0 : 0.32 : 1.3.

Diet No. 4 (calorie value = 2,200)

6 a.m.—Tea, 10 oz.; milk, 2 oz.

8 a.m.—Underdone beef, 6 oz.; rusks, $1\frac{1}{2}$ oz.; calves-foot jelly, 2 oz.; juice of 1 orange + glucose, 2 drachms.

10 a.m.—1 baked apple + custard, 2 oz.

12 noon.—Soup, 5 oz. + liver extract (= $\frac{1}{4}$ lb.); underdone beef, 7 oz.; calves-foot jelly, 2 oz.; rusks, 3 oz.; juice of 1 orange + glucose, 2 drachms.

4 p.m.—Tea, 10 oz.; milk, 2 oz.; 1 baked apple; custard, 3 oz.

7 p.m.—The same as at 12 noon, but only $1\frac{1}{2}$ oz. of rusks allowed.

Protein : fat : carbohydrate = 1.0 : 0.34 : 1.3.

Diet No. 5 (calorie value = 3,020)

6 a.m.—Tea, 10 oz.; milk, 2 oz.; glucose, 2 drachms; rusks, $1\frac{1}{2}$ oz.; butter, 1 drachm; one scraped ripe apple or one fully ripe canary banana (yellow ends).

8 a.m.—Underdone beef, 7 oz.; rusks, 3 oz.; calves-foot jelly, 2 oz.; juice of 1 orange + glucose, $\frac{1}{2}$ oz.; honey, 2 drachms; butter, 1 drachm.

10 a.m.—1 baked apple; custard, 3 oz.

12 noon.—Soup, 5 oz. + liver extract (= $\frac{1}{4}$ lb.); underdone beef, 7 oz.; calves-foot jelly, 2 oz.; rusks, $1\frac{1}{2}$ oz.; juice of 1 orange + glucose, $\frac{1}{2}$ oz.

4 p.m.—Tea, 10 oz.; milk, 2 oz.; glucose, 2 drachms; rusks, 3 oz.; baked apple, 1 oz.; custard, 3 oz. (egg boiled or poached sometimes substituted); honey, 2 drachms.

7 p.m.—The same as at 12 noon.

Protein : fat : carbohydrate = 1.0 : 0.36 : 2.0.

Routine.—The patient must be confined strictly to bed during the first few stages of the treatment, as bodily and mental rest are as important as in the treatment of duodenal ulcer, for example. If possible, the patient should be in an institution and should also have a special day nurse unless the institution is very well staffed. If treated at home, he must have a day and a night nurse, and the former should be carefully selected, and, if possible, should have had previous experience of sprue.

The first stage of the diet should be adhered to for *at least* ten days, in severe cases for a fortnight, and even then the second stage must only be started if all the main symptoms have subsided. The same rule applies for each stage of the diet, and, whenever there is any relapse of symptoms, the patient must be put back at least one stage, and, if the relapse is a serious one, back to the first stage.

The patient may be allowed to get up for defæcating and washing during the fourth stage, and to sit up in a chair for part of the day during the fifth stage.

The injections of liver extract (the whole-liver extracts are usually better than the more refined ones, and they must be given in generous doses) and niacin, if they are indicated, should be given early.

Marmite, or some other autolysed yeast preparation, and vitamin-A and -D concentrates should be given by mouth, and additional calcium in the form of calcium lactate or basic triple phosphate in doses of a drachm thrice daily.

Cortin appears to aid fat absorption in some cases, and should be given a trial.

Symptomatic treatment.—A purgative may be given at the commencement of treatment, a full dose of castor oil, or pulv. rhei co. If there is any tendency to constipation, ispaghula (*Plantago ovata*) *bhusie*, obtainable in the bazar in India, or the proprietary preparations, normacol or isogel, should be given regularly. If these fail, pulv. glycyrrhizæ should be given in preference to liquid paraffin, which may further interfere with the effective absorption of vitamins. The atonic condition of the bowel may have led to a constipated condition in which there are large fæcoliths in the bowel that may necessitate warm oil enemata for their removal.

It is probably not advisable to interfere too much with the looseness of the bowels if it occurs in the early stage before treatment has had time to take effect, but later, if the diarrhœa is troublesome or disturbs the patient at night, kaolin or bismuth should be given. A course of

sulphapyridine produces surprisingly satisfactory results in some cases of obstinate diarrhoea.

For flatulence and indigestion, a mixture of spiritus ætheris nitrosi and spiritus ammoniæ aromaticus, 15 minims of each in half an ounce of peppermint water, should be tried first, but if the indigestion persists, in view of the low acidity, an alkaline mixture should be given before meals and dilute hydrochloric acid one half increasing to one drachm well diluted with water after meals.

When there is gross emaciation, intravenous glucose, 200 c.cm. of a 25 per cent solution of glucose together with 10 units of insulin, and, for cramps or tetany, parenteral calcium and parathyroid by mouth, should be given.

For meteorism, turpentine in minim doses, turpentine stupes, and finally pituitary extract should be given, but some modification of the diet may be necessary, especially when milk is being taken.

Special care should be directed towards the mouth. A potassium chlorate mouth-wash, a drachm to the pint, or optochin, should be used, or, if the mouth is painful, glycerine and borax, with 2 grains of cocaine to the ounce in extreme cases when the soreness is interfering with the taking of nourishment.

Convalescence.—Exercise must be graded carefully, and the patient should not be allowed to return to full work for two or three months. 'Home' leave is the ideal solution, if it is during the summer, but an extremely cold climate will be as unsatisfactory as a hot one. The question will arise as to whether the patient should go to the 'hills'. If he has shown no particular susceptibility to hill residence (*see* HILL DIARRHOEA) there is nothing against this, but, if some healthy plains climate is within easy reach, this will be preferable. The popular sea trip must depend on whether the food and accommodation is likely to be entirely satisfactory.

Diet is of course most important, and the patient must endeavour still to follow the general principles of the diet that brought him back to health. The fat intake should be restricted for several years, and skimmed milk or 'sprulac' should be taken several times during the day.

Spirits, except possibly once in the evening, should be avoided, but wines or beer may be taken with meals, naturally in moderation.

Prevention.—It would be impossible to lay down any satisfactory rules for prevention. However, sprue is probably less common amongst sojourners who live on a good mixed diet with the vitamins all well represented. Food-faddism is very dangerous in the tropics, but a careful study of the diet, based on established scientific data and not on the ideas of some 'popular' medical writer, should be encouraged in persons who show some tendency to develop sprue. If this tendency continues to develop despite this, that individual should be recommended to return to a temperate climate, where for some time he may still have to consider his diet. The long continuance of restricted diet is also a precipitating factor and must be guarded against. If such a diet is inevitable, then extra vitamins must be given.

Prognosis.—This is dependent on the stage at which the patient comes under observation, the co-operation of the patient, and the facilities for proper treatment. If the treatment is undertaken early, the prognosis should be good, but it may be necessary for the patient to leave the tropics; this is particularly the case if the symptoms developed after short residence, as it will indicate that the patient is particularly predisposed to the condition.

At the other end of the scale, if a patient is grossly emaciated with a distended abdomen, has serious macrocytic anæmia, and is unable to take

solid food on account of extreme soreness of the mouth, the prognosis is grave, but not hopeless if conditions for treatment are optimal.

REFERENCES

- ASHFORD, B. K. (1929) .. Mycology of the Intestinal Canal in Porto Rico and its Relation to Tropical Sprue. *J. Amer. Med. Assoc.*, **93**, 762.
- CANTLIE, J. (1913) .. Colloidal Argentum: Its Use in Sprue and Post-Dysenteric Conditions. *J. Trop. Med. and Hyg.*, **16**, 123.
- CASTLE, W. B., and RHOADS, C. P. (1932). The Aetiology and Treatment of Sprue in Porto Rico. *Lancet*, **i**, 1198.
- ELDERS, C. (1919) .. *Nederl. Tijdschr. Geneesk.*, **63**, 1683.
- FAIRLEY, N. H. (1930) .. Sprue: Its Applied Pathology, Biochemistry and Treatment. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **24**, 131.
- Idem* (1939) .. Sprue, Tropical. *British Encyclopædia of Medical Practice*, **11**, 419. Butterworth and Co., Ltd., London.
- HANES, F. M. (1942) .. Diagnostic Criteria and Resistance to Therapy in the Sprue Syndrome. *Amer. J. Med. Sci.*, **204**, 436.
- HURST, A. (1942) .. Pathogenesis of Sprue Syndrome as seen in Tropical Sprue, Non-Tropical Sprue and Celiac Disease. *Guy's Hosp. Rep.*, **91**, 1.
- LEITNER, Z. A. (1942) .. The Physiology of the Small Intestine: Its Application to the Aetiology of Sprue. *Trop. Dis. Bull.*, **39**, 497.
- MACKIE, F. P., and CHITRE, G. D. (1928). Animal Experiments and Sprue. *Indian J. Med. Res.*, **16**, 49.
- MACKIE, F. P., and FAIRLEY, N. H. (1934). Gross and Microscopic Anatomy of the Intestinal Canal from Two Cases of Sprue. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **27**, 340.
- MACKIE, T. T., and POUND, R. E. (1935). Changes in the Gastro-Intestinal Tract in Deficiency Cases, with Special Reference to the Small Intestine. Roentgenologic and Clinical Study of 40 Cases. *J. Amer. Med. Assoc.*, **104**, 613.
- MANSON-BAHR, P. (1939) .. *The Dysenteric Disorders*. Cassell and Co., Ltd., London.
- McCARRISON, R. (1919) .. The Pathogenesis of Deficiency Disease. *Indian J. Med. Res.*, **7**, 283.
- PASRICHA, C. L., and LAL, S. (1939). Incidence of Monilias in Human Fæces. *Indian Med. Gaz.*, **74**, 682.
- THAYSEN, T. E. H. (1931) .. Pathological Anatomy of the Intestinal Tract in Tropical Sprue. *Trans. Roy. Soc. Trop. Med. and Hyg.*, **24**, 539.
- VEDDER, E. B. (1940) .. A Discussion of the Aetiology of Sprue. *Amer. J. Trop. Med.*, **20**, 345.

PARA-SPRUE

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Definition.—Para-sprue is a disease of dietary origin in which there is a watery diarrhoea of long duration, loss of weight, a sore red tongue, and later marked macrocytic anæmia; it occurs in the European sojourner, the domiciled European and Eurasian, and the native, in the tropics.

ÆTIOLOGY AND EPIDEMIOLOGY

The writer believes that the disease is basically dietetic, but that both dysentery, in its direct effect on intestinal absorption and in encouraging a limitation of diet, and malaria, in its predatory effect on the red cells with consequent exhaustion of essential hæmopoietic material, are very frequent contributory or determining factors (Napier, 1939).

It occurs mainly in poorer Indian, and other native, populations living on a low diet, deficient in good protein and vitamins, especially of the B₂ group, in which malaria and bowel disorders are common, but it also occurs in the better-dietary groups when, as a result of some bowel disorder, a patient is kept on a low fluid diet for a long time; it is found amongst pregnant women (Napier and Edwards, 1941). It also occurs in poorer-class Europeans and Eurasians, and in economically-higher classes of these two groups following long continued bowel disturbances.

PATHOLOGY

Little is known of the morbid anatomy of this condition.

Blood.—A macrocytic anæmia is the rule in the later stages of this condition; the red cell count may drop to a million and a half, or even lower. There is also usually a leucopenia. The sternum-puncture count usually shows a slight increase of megaloblasts (non-hæmoglobinized, basophilic cytoplasm, with a finely stippled lightly-stained nucleus) but not a true megaloblastic reaction.

The glucose absorption curve is usually low or normal, but occasionally it will be completely flat, indicating practically no carbohydrate absorption.

Gastric analysis.—This is often normal, but there may be hypochlorhydria, or more frequently a pseudo-achlorhydria that responds to histamine; occasionally true achlorhydria has been found, but this also occurs in about 4 per cent of normal persons.

Stools.—They are usually watery and light in colour, but not the bulky, frothy and pale stools of sprue; there is often some increase of fat, but the total fat is seldom above 30 per cent of the weight of dried fæces, with the normal proportion of split fat.

SYMPTOMATOLOGY

The onset is usually gradual, following a period of ill health as indicated above. In the fully-developed case, there is emaciation, a sore red tongue, sometimes a low fever, anæmia with its accompanying signs and symptoms, and diarrhœa without any localizing abdominal symptoms. There is also usually dyspepsia, flatulence, and abdominal discomfort. Oedema of the legs is also common; this usually improves with rest in bed. As long as the patient is kept on a poor fluid diet, the diarrhœa will continue and the anæmia increase, until the patient dies as a result of the anæmia, or of some concomitant infection.

Diagnosis.—There is no clear-cut method of diagnosis. The absence of the extreme degree of emaciation, the tumid lower segment of the abdomen, the parchment-like skin, the severe dysphagia, and the bulky, frothy pale stools with an increase of fat above 40 per cent exclude true sprue, and the absence of the dermal lesions and mental symptoms exclude pellagra. Ulcerative colitis can be excluded by the absence of red cells or cellular exudate in the stools. Intestinal tuberculosis and malignancy have to be considered; in the former condition, tubercle bacilli can often be found by examination of a smear, but more recent methods include animal inoculation of an antiformin-treated specimen; in the latter there will usually be occult blood.

TREATMENT

The treatment of para-sprue is very much that of sprue, except that no strict dietary regime is necessary. We usually encourage the patient to take the full mixed hospital diet (which includes meat), and this is, if possible, supplemented by eggs, extra milk and marmite. While it is unnecessary to restrict fat rigidly, care should be taken that the meat is not served swimming in fat, as Indian cooks are liable to serve it, and, in fact, special attention should be paid to the cooking and serving of the food.

Liver extract constitutes the most important specific item, and this should be given in full doses of one of the whole-liver (or crude) extracts. The blood picture improves immediately, with a sub-maximal reticulocyte response.

For the diarrhœa, treatment for not more than two days with sodium sulphate in drachm doses four-hourly is followed by kaolin or a bismuth mixture, if necessary, until it stops, but quite often the stools will become formed directly the diet is changed from the low-calorie fluid diet that the patient was taking in his home to a well-balanced solid diet.

Sulphapyridine is sometimes surprisingly efficacious in stopping the diarrhœa, presumably because it cures the mild inflammatory condition from which the ill-nourished mucous membrane is suffering. One would expect the new, less soluble drugs, such as sulphanilyl-guanidine, to be even more efficacious.

If there is achlorhydria, hydrochloric acid should be given with each meal. Attention should be paid to associated infections, particularly malaria and intestinal helminth infections. For anæmic patients, a blood transfusion appears to have a tonic effect far beyond that of simple blood replacement.

Prognosis.—With adequate treatment this is usually good, and if the response is not rapid, one should question the diagnosis, and again consider such conditions as ulcerative colitis or intestinal tuberculosis.

HILL DIARRHŒA

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Discussion.—The literature on hill diarrhœa goes back nearly a hundred years; it presents a kaleidoscopic series of pictures of the possible or probable ætiology of this condition, which all seem totally disconnected, each writer's contribution being mainly destructive of previous theories and presenting very little in the way of constructive contribution to the problem. Some of the theories that were put forward were that it was a form of scurvy—even at that time (1854) known to be due to lack of fresh fruit and vegetables, that it was a disorder of the liver due to the low temperature, and that it was due to the presence of mica in the water.

Ætiology.—It seems very likely that the expression 'hill diarrhœa' covers as many bowel disorders as would the word 'diarrhœa' used at any other level; its ætiology is probably as varied.

The main root cause of hill diarrhœa in India is, in the writer's opinion, a curious lethargy that affects the sanitary sense of the administrator in India when he transfers his activities to the holiday atmosphere of a hill station. Nearly all hill stations are appallingly insanitary, and much of the diarrhœa is due to mild *Bact. flexneri* infections acquired through water, milk, or food, particularly the latter which is usually infected by flies. The definite epidemics that were reported by the early writers, and which frequently occur now, indicate the infectious nature of the disease. Another cause is undoubtedly the reactivation of a chronic dysenteric condition by sudden subjection to the damp cold of a hill station; the history given is so frequently an onset immediately the subject arrives in the station. A third suggestion is that the sudden subjection to the cold causes a failure of the proper 'pumping action' of the villi and thereby defective fat absorption, but this does not explain why the same thing does not happen when the subject goes to a cool climate at sea level. But there is a fourth class of case which does not quite fit any of these suggested ætiologies, namely that of the patient who gets an attack of diarrhœa only when he (or she) goes to the hills; this attack continues more or less throughout the visit—certainly if this is a short one—and disappears immediately on his return to the plains; and this patient does not suffer in the same way when he returns to a cold climate in Europe. This only constitutes a very small percentage of the cases of hill diarrhœa, but the writer believes that such cases do occur, and that the low atmospheric pressure may be the cause.

One very definite physiological change that occurs at high altitudes in an increase in hæmoglobin percentage to counteract lower oxygen tension. To meet the immediate emergency, the red cell reservoir in the spleen will be emptied and there will thus be a reduction in the number of cells undergoing the pre-hæmolysing process in this organ, with consequent reduction in blood destruction; as a result of this, there will naturally be decreased bile production. Another way the relative shortage of red cells can be supplied is by increased production; it seems possible that the increased

demand for the raw material for additional blood formation might lead to a lower rate of wastage and again decreased bile formation. Decreased bile will lead to a decrease in fat and calcium absorption, and an unhealthy condition of the bowel content. The adaptability of the individual naturally varies, so that these reactions will be more apparent in some subjects than in others.

Symptomatology.—This will naturally vary according to the cause. The usual experience is a watery diarrhœa, which starts very soon after the patient reaches the hill station, and is accompanied by mild constitutional symptoms; microscopical examination shows a cellular exudate but seldom any blood, suggesting a mild bacillary dysentery.

In true hill diarrhœa—if there is any such condition caused by the climatic effects only and the writer believes that there is—the stools are very similar to those of sprue; the main defect is an increase of fat which in some cases is associated with a deficiency of bile. There will be a large fluid, fatty and frothy stool first thing in the morning, and diarrhœa usually up to about midday, after which there are no more stools until next day. There is marked flatulent dyspepsia—not an uncommon experience in arrivals at a hill station—and a certain amount of lassitude, but otherwise the subject does not feel particularly ill, and he is able to enjoy, but not to the full, his holiday, or to carry on his work, as the case may be.

Treatment.—The treatment of the infective type is with sodium sulphate in 2-drachm doses every four hours during the first day or two, followed by kaolin or bismuth, as in mild forms of bacillary dysentery. More severe forms may require sulphapyridine or sulphanilyl-guanidine.

The 'climatic' form will respond best to dietetic treatment, namely, the reduction of fat, on the lines of the treatment of sprue, but it will seldom be necessary to put the patient on the earlier stages of the diet, in fact, the fourth stage (*see* table X, p. 474) will usually suffice; calomel in divided doses ($\frac{1}{4}$ grain half-hourly up to $1\frac{1}{2}$ grains) should be given for the first night, and bile in the form of keratin-coated pills, gr. x, thrice daily, for several days.

The classical treatment for this condition was a drachm of liquor hydrargyri perchloridi, thrice daily after food, followed by 10 grains of pepsin two hours later.

LEPROSY

by
John Lowe, M.D.

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Introduction.—In the last two decades it has become increasingly realized that in different countries there are marked variations, not only in the incidence, but also in the severity of leprosy. In some countries, *e.g.* parts of India and of Africa, leprosy is very common but often mild. In other countries, *e.g.* parts of the Philippine Islands and of South America, the disease is less common but considerably more severe. In still other countries, *e.g.* parts of South China, of Burma, and of South America, the disease is both common and severe.

An unbalanced and depressing view of leprosy may be the result of studying leprosy in countries where the disease is usually seen in severe forms, and particularly when such studies are largely confined to severe cases seen in leprosy institutions. Such studies appear however not infrequently to have formed the basis of accounts of leprosy in medical literature.

The description of leprosy given here is based on long experience of leprosy in the general population of India, supplemented by experience gained in brief visits to other countries, and by a thorough study of the literature of the disease.

In most parts of India, the milder neural type of the disease predominates, and slight abortive cases of leprosy are common; even the cases of the severer 'lepromatous' type are frequently less severe and progressive than those seen in some other countries. It will, therefore, be found that the picture of leprosy presented here is on the whole less depressing than that frequently presented in medical literature. The disease is *not* described as highly infectious, nearly always progressive, and sooner or later but invariably fatal.

It is however believed that the description given here can be applied, with minor modifications, to leprosy in any country, and that probably nowhere in the world is the prognosis of leprosy so hopeless as is often suggested.

Definitions.—Leprosy (Synonyms:—*Lepra*, *Elephantiasis Graecorum*, *Lepra Arabum*) is a disease belonging to the group 'infective granulomata', is caused by *Mycobacterium lepra*, and is transmitted from man to man, mainly if not entirely, by contact; it is endemic in varying degree in most tropical and sub-tropical countries, and it was endemic in the past, but is so to a much less extent at present, in some temperate countries; it occurs in two main forms now called 'neural' and 'lepromatous'; and it is characterized by extreme chronicity.

The **neural type** is relatively mild, and the lesions are confined to certain areas of skin and/or to certain peripheral nerves and the tissues supplied by them. The **lepromatous type** is relatively severe and progressive, and the lesions are usually widespread in skin and mucous membranes, and to a less extent in the internal organs; the vital organs however show little or no affection.

The definition of these two main types of leprosy adopted at the International Leprosy Congress, 1938, was as follows:—

'**Neural (N) type.**—All cases of the "benign" form of leprosy with disturbances of polyneuritic nature (i.e. alterations of peripheral sensation, trophic disturbances, atrophies, and paralyses, and their sequelæ), or macules of a non-lepromatous nature (i.e. leprides, usually with localized sensory disturbances), or both. These cases give evidence of relative resistance to the infection, are of relatively good prognosis as regards life although mutilation may take place, and usually react positively to lepromin. Bacteriologically, the skin lesions are typically but not invariably found negative by standard methods of examination, though the nasal mucosa may be found positive*. Many of these lesions are histologically of a "tuberculoid" nature'.

'**Lepromatous (L) type.**—All cases of the "malignant" form of leprosy, relatively non-resistant and of poor prognosis, usually negative to lepromin, exhibiting lepromatous lesions of the skin and other organs; especially the nerve trunks. Bacteriological examination usually reveals abundant bacilli. Disturbances of polyneuritic nature may or may not be present; they are usually absent in the earlier stages and present in the later stages of primarily lepromatous cases, and often present in cases arising secondarily from the neural form'.

Some of the points made and the terms used in these definitions are later explained more fully.

* In our experience the nasal mucosa in true neural cases shows no bacilli.

HISTORICAL

Leprosy in ancient medical writings.—The earliest references to leprosy confirmed by clinical descriptions are in the ancient literature of India; the *Sushruta Samhita* (about 600 B.C.) contains definite references to, and descriptions of, leprosy, but there are other probable references in still older Indian literature. The supposed references to leprosy in ancient Egyptian, Jewish, and Chinese writings of the pre-Christian era are of doubtful authenticity, no definite clinical details indicating leprosy being given, but this fact does not prove that leprosy was not prevalent in ancient times in the countries in question. In most ancient medical literature, the definite recognition of the disease now called leprosy is difficult or impossible, partly because words which now mean leprosy were sometimes used in ancient writings either with a much wider meaning or else with a different meaning; for example the Sanskrit word *kushtha*, which is now generally used for leprosy, originally meant skin disease in general; the Greek word '*lepra*' from which name 'leprosy' is derived, originally meant a scaly disease, possibly psoriasis, and was only later applied to leprosy, as the result of mistakes in translation.

The disease was possibly mentioned by Hippocrates, and certainly mentioned and described by later Greek writers, Lucretius, Celsus in the first century B.C., and by numerous later authors in Greco-Roman times. These writers first mention leprosy as a disease rare in Italy but more common in the eastern Mediterranean. Later, the spread to Italy and to other parts of Europe is recorded by contemporary writers.

With the collapse of the Greco-Roman civilization, the science of medicine retrogressed and was largely forgotten in Europe, but the Greek medical knowledge was kept alive by the Arabians, who studied the Greek and probably the Indian writings on leprosy, and wrote extensively themselves on the subject. The Greek writings on leprosy were recovered to Europe first indirectly from the Arabian writers by the writers of the school of Salerno in Italy in the tenth century, and, later, directly through the recovery of the ancient Greek writings themselves.

During this time the terminology of leprosy became confused, and it took many centuries to clear up this confusion.

Both the Greek and the Arabian writers had used both the terms *lepra* and *elephantiasis* but with completely different meanings. The Greeks, as already stated, used the word *lepra* possibly for psoriasis, while for our leprosy they used the word '*elephantiasis*' (because the thickness and texture of the skin of severe cases of leprosy was thought to resemble that of the elephant's skin); whereas the Arabians had translated '*lepra*' as meaning our leprosy (Arabic *juzahm*) and they interpreted *elephantiasis* as filariasis (Arabic *dil-fil*).

The medical writings on leprosy in Europe in the Middle Ages were dominated very largely by the Greek writings, and contain little original material. Dozens of descriptions of leprosy were, however, written in the countries of Europe. Under the impression, possibly a mistaken one, that the terms *zaraath* (Old Testament Hebrew) and the *lepra* (New Testament Greek) indicated leprosy, the disease then common in medieval Europe, the word 'leprosy' was used in translating the Bible into some (but not all) European languages, and the Mosaic Law relating to *zaraath* was applied to the medieval leprosy.

Leprosy in modern medical writings.—The developments of scientific and medical knowledge which later followed the Renaissance were not for a long time applied to a study of leprosy, partly because by that time there was little leprosy left in Europe. It was only in the nineteenth century that the Norwegian workers Danielssen and Boeck, and later Hansen made the studies which led to the scientific work on leprosy,

especially in the last forty years. This work has established leprosy as a disease showing many points of resemblance to tuberculosis, and also some important differences.

To the modern literature of leprosy, workers of many nations have made notable contributions.

The scientific study of leprosy initiated in Norway by Danielssen and Boeck, was continued by Hansen and Looft, and later by Lie and others. Other workers in Europe have included Virchow, Unna, Arning, Ehlers, Marchoux, Jadassohn, Jeanselme, Klingmuller, Hutchinson, Radcliffe-Crocker, Paldock, Tonkin, Hoffmann, Stein and others.

Numerous United States workers have studied leprosy in America, Hawaii, or the Philippine Islands; amongst these workers are included Dyer, Hopkins, Denny, Dean, Hollman, Macdonald, Heiser, McCoy, Aycock, McKinley, Soule, Wayson, Wade, Cole and Hesseltine.

In the Philippine Islands, Filipino workers include Rodriguez, Lara, Nolasco, Manalang and Chiyuto.

In India, organized leprosy research was initiated by Rogers and carried on by Muir. Later workers include Chatterji, Cochrane, Dharmendra, Henderson, Lowe and Santra.

In Japan, leprosy workers have been very numerous and have included Sugai, Ota, Sato, Asami, Mitsuda, Hayashi and Uchida.

In South America, in recent years, leprosy work has much developed and among the writers have been De Souza Araujo, Balina, Fernandez, Fidanza, Schujman, De Souza Campos, Rotberg, and Rebello.

In the French colonies have worked Delinotte, Tisseuil, Montel and others, in the Dutch colonies, de Langen, Lampe, and Sitanala, and in the Belgian colonies, Dubois, Degotte, and Radna.

In Australia, workers have included Ashburton Thompson, Cilento and Molesworth; in South Africa, Moiser, Mitchell, and Strachan.

In other parts of the British Empire, Frazer and Ryrie (Malaya), Rose (West Indies), Simon (Ceylon) and Austin (Fiji) have worked on this subject.

In China, workers have included Maxwell, and in Korea, Wilson.

The writings of these and many other workers are largely contained or abstracted in *Leprosy Bibliotheca Internationalis* (1900 to 1914) and the *International Journal of Leprosy* from 1933. These publications, and also the other publications mentioned in the bibliography, have been used in the preparation of the present chapter, but it has been considered inadvisable to burden the text with hundreds of references. A select bibliography is given at the end of the chapter.

The history of the disease.—This has already to a considerable extent been outlined in the preceding discussion. Leprosy has been common in India, and probably in Africa and China for many centuries. In classical times, leprosy invaded the Mediterranean countries and later it spread over most of Europe including the British Isles. For about a thousand years it was common in these areas, and then, between the fourteenth and sixteenth centuries, it declined markedly, although it persisted and still persists in some foci in Europe, chiefly in the countries bordering the Mediterranean, and to a less extent in Iceland, Scandinavia, and the Baltic countries.

The decline of leprosy in medieval Europe has been attributed to segregation measures, to improved hygienic conditions and diet, to climatic changes, and to the development of racial immunity. None of these explanations appears to fit the facts.

The disease was imported by immigrants from Europe and by slaves from Africa to the American continent, where previously there was no leprosy. In North America, it has persisted, chiefly in the southern states but only to a very limited extent, and mainly in people of European descent. In Central and South America, however, it has steadily increased and is now very common in certain areas, particularly north Brazil, and both Europeans and negroes are affected. The Indians of both North and South America have very little leprosy.

More recent still is the spread of leprosy to Australasia and the Pacific area. Here Chinese immigrants have played an important part. In Australia the disease has become endemic only in the north, chiefly in Queensland, but a few cases are found in other areas, both white and coloured people being affected.

In the Pacific, within the last century, leprosy has assumed epidemic proportions in certain islands, notable examples being New Caledonia where it affected not only the local people but also the large French penal population, Hawaii where it became very common among the Hawaiians, and most striking of all, Nauru, a small island in the South Pacific, where within a few years of the introduction of leprosy, 30 per cent of local inhabitants showed signs of the disease. In practically all these areas, however, leprosy is now on the decline, this decline being possibly caused, and certainly accelerated, by control measures.

The history of leprosy, therefore, is one of persistent endemicity in many tropical and sub-tropical countries, with periods of invasion into temperate and even cold climates, these periods however being sometimes of very long duration.

ÆTIOLOGY

The causal organism.—The causal organism of leprosy belongs to the genus *Mycobacterium*, which occupies a position midway between the bacilli and the fungi. It is rod-shaped, varying considerably in length from 2 to 8 microns, and in breadth from 0.5 to 1 micron. It is usually straight or slightly curved, and it frequently shows in its protoplasm dark staining granules, which may be multiple and small, and distributed evenly along the length of the organism, or may be single and large, occupying either the middle or the end of the organism. The bacillus is stained readily by the Ziehl-Neelsen technique, that is to say it is acid-fast, and it is gram-positive.

In active lesions of the neural type, the bacillus is found, but often only with great difficulty. In lesions of the lepromatous type, the bacilli are very numerous, and they show a marked tendency to occur in round masses, *globi*, which occupy large vacuolar spaces in the infected cells. It is this characteristic which enables a distinction to be made between the tubercle bacillus and the leprosy bacillus in the tissues. In other respects the organisms are morphologically identical.

Culture.—In the sixty odd years since the organism was first discovered, thousands of attempts have been made to cultivate it *in vitro*, but even with all the refinements of modern bacteriological technique, it is extremely doubtful whether any true culture has been obtained. A few workers have claimed success, but no such claim has obtained any wide acceptance.

Animal inoculation.—Many attempts to infect animals with the organism have been made, with similarly unsatisfactory results. The injected bacilli can produce lesions at the site of inoculation and also elsewhere, but there is usually no definite evidence of multiplication or of generalization of the disease. It appears that, up to the present, the only animal found susceptible to the organism is man. Numerous attempts at experimental inoculation of human beings have been made, with positive results in a few, but the conditions of the experiments have not been entirely satisfactory. The large number of negative results may possibly be due to the fact that the experiments have been carried out in adults, who are usually immune.

Viability.—In the circumstances outlined above, we have very little evidence regarding the viability of the organism, and it is impossible to say

whether it is killed easily or with difficulty, whether it can exist in a living condition outside the body, and, if so, for how long, and under what conditions. From analogy with other acid-fast organisms, we may surmise that it is killed with difficulty by antiseptics, but killed rather easily by heat and by drying.

Causative relationship to leprosy.—As indicated above, Koch's postulates have not been fulfilled, and the proof of the causative relationship of *Mycobacterium lepræ* to the disease is incomplete; nevertheless this relationship is generally accepted.

The rarity of the acid-fast bacilli in many cases of the neural type has led to the suggestion that the acid-fast bacillus is only one phase of development of the organism, and that, in other phases, the organism may be non-bacillary and non-acid-fast. Evidence to support this view is very scanty and unconvincing, and general opinion is against it.

It has been suggested that the two main types of leprosy are so different that they are caused by different strains of the organism. This, however, is probably not so, since the neural type can, without any fresh infection, develop into the lepromatous type, the change taking place being not in the organism itself, but in the reaction between the organism and the tissues.

Transmission.—In the absence of a susceptible animal for transmission experiments, knowledge of this subject is limited, and is based mainly on observations of the transmission of the disease in infected populations. The usual, if not the only, mode of transmission appears to be contact (usually direct though possibly indirect but close) of open cases of leprosy with healthy persons. While it is true that close continued contact is most favourable to transmission, there is evidence to indicate that some highly susceptible persons may develop the disease from very limited contact.

The mode of entry of the bacilli into the body is not known for certain. It may be inoculated through cuts, abrasions, or insect bites in the skin, by rubbing or scratching the skin. Infection may possibly occur through mucous membrane.

Congenital infection does not occur. Infection *in utero* has occasionally been reported (at post-mortem examination) but it can very rarely be followed by the development of the disease, for children separated at birth from leprous parents practically always remain healthy. The general opinion is that transmission by air, by food and water, by biting insects and infected articles is rare, and in the opinion of some, impossible. It is not impossible that transmission is influenced by environmental conditions including climate, possibly by its influence on the viability of the bacillus outside the body.

The old idea that all cases of leprosy are infectious has been abandoned. The general idea now is that only those patients in whom bacilli can be demonstrated by the methods of examination described later should be regarded as infectious cases. The bacteriologically positive cases are generally, but not always, cases of the lepromatous type. A few neural cases may be bacteriologically positive, but usually only to a limited extent and for limited periods. This differentiation of open cases from closed cases is important in preventive work.

The idea has, however, occasionally been suggested that, even though bacilli cannot be demonstrated in them, the neural cases may be infective. Such ideas are usually based on the fact that many patients with leprosy deny all knowledge of contact with open cases. This difficulty is a real one, but it may be explainable by the fact that the latent period is often very long, that accurate histories covering such a long period are difficult or impossible to obtain, and that many cases of leprosy, even open cases, are not known as such to others. In a recent epidemiological study carried on

in villages in one part of India, in 80 per cent of the new cases arising during the period of the study, infectious contact could be proved.

Strong support of the view that closed cases are not infectious has been afforded by a recent careful epidemiological survey carried out in the Philippine Islands, in which it was found that the incidence of leprosy in the family contacts of 'closed' cases was actually lower than the incidence of leprosy in the general population with no known contact, while in contacts of open cases the incidence was, of course, much higher.

IMMUNOLOGY

There is no doubt that the degree of natural susceptibility to leprosy in different persons varies considerably. Under 'Epidemiology' the various factors which may have an influence in this matter are discussed.

There is also considerable evidence (*vide infra*) that acquired specific immunity to leprosy occurs, but there is no completely specific test for such immunity. There appears to be, however, a definite element of specificity in the lepromin test.

The **lepromin test** was originated over thirty years ago by Mitsuda, and consisted of the intra-dermal injection of a minute amount of an emulsion made by grinding up lepromatous tissue, rich in bacilli, and previously sterilized by boiling. A positive result is indicated by the development, during the next few weeks, of a small nodule at the site of injection. A positive result is commonly seen in cases of the neural type, particularly 'tuberculoid' cases, in healthy contacts, particularly adults, and in some healthy non-contacts, particularly adults. A negative result is seen in cases of the lepromatous type, and in healthy young children, contacts or non-contacts. The completely negative result seen in cases of lepromatous type is a striking feature of the test, and it is possibly analogous to the negative result seen in some very advanced cases of tuberculosis.

Numerous later workers, particularly Dharmendra, have introduced improvements in the methods of preparing lepromin, standardizing the dose and reading the results. The active principle of the emulsion has been shown to be the bacilli, and methods have been evolved of obtaining bacilli free from tissue and of standardizing by a bacillary count, or still better by weight.

Recently Fernandez has shown, and others have confirmed, that the late nodular reaction is preceded by an early (24/48 hours) reaction of the 'tuberculin' type which is of the same significance as the late nodular reaction. It has moreover been found that by breaking down the bacilli by physical methods, defatting and grinding, the early reaction can be enhanced, and the late nodular reaction can be almost abolished. Dharmendra has isolated and tested all the chemical fractions of the bacilli, has found that the antigen is of a protein nature and gives rise to the early reaction only, has shown that the late reaction is caused by this protein fraction being slowly liberated from the unbroken bacilli, and has attempted to isolate a specific antigen. This result has not been obtained, but by using small doses of antigen, the number of positive results in non-contacts has been much reduced, without any appreciable reduction in the number of positive results in neural cases.

There appear to be two factors contributing to a positive result in the lepromin test, one specific and the other non-specific, and, so far, it has been impossible entirely to eliminate the non-specific factor. Until this is done, the test is likely to be of very little value in diagnosis.

In prognosis, however, the value of the test is considerable. In healthy contacts, a definite positive result is an indication either that leprosy will

not develop, or that the disease will be of the mild neural type. In cases of neural type, it indicates a relatively good prognosis and the unlikelihood of development into the lepromatous type. In cases of the lepromatous type, very few positive results are seen, but when seen may indicate a prognosis better than usual in such cases.

The following is a brief account of the methods of preparing lepromin, doing the test and reading the results :—

By the older methods, lepromin was prepared by grinding leprous nodules in saline and diluting until the bacillary concentration was roughly the same as in a previously used and satisfactory preparation, or until the injection of 0.1 of a c.cm. produced a significant but not excessive reaction in a case of neural type and no reaction in a case of lepromatous type. By thorough grinding and centrifugalization, it is sometimes possible by such methods to produce a suspension which can be standardized by a rough bacterial count.

The latest methods involve a separation of the bacilli from the nodular material either by centrifugalization in fluids of different specific gravity or by extraction with chloroform (for details see Dharmendra, 'Leprosy in India', 1942, p. 122). Such preparations can be standardized by weight.

A dose of two million bacilli, or 0.01 mgm. by weight of the bacillary powder, suspended in saline is injected intra-dermally as in the tuberculin test.

The readings are as follows :—The early reaction is seen in 24 or 48 hours and consists of an area of swelling and erythema $\frac{1}{2}$ inch or more in diameter. The late reaction seen from the second week and usually at its maximum between three to four weeks takes the form of a definite nodule in the skin, easily palpable, and usually measuring 5 mm. or more in diameter when held with the skin between the jaws of a measuring instrument.

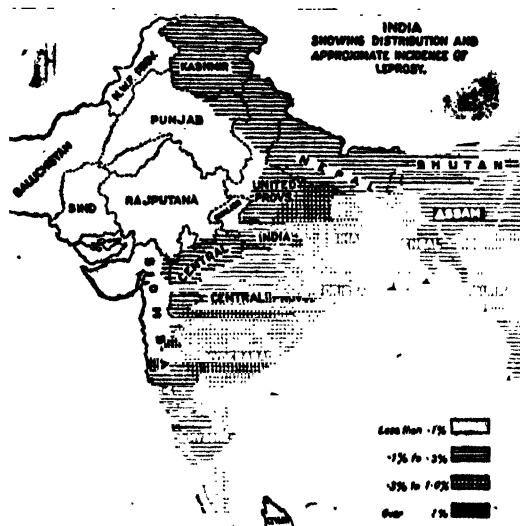
Complement fixation may be seen in leprosy. The sera of certain cases of leprosy have the power of fixing complement in the presence of certain antigens, *e.g.* Wassermann antigen, and antigens prepared from various acid-fast bacilli including those of tuberculosis and leprosy. This fact is of no practical value in diagnosis or prognosis. It is a curious fact that complement fixation is seen commonly in the more severe (lepromatous) form of leprosy in which the lepromin test gives negative results.

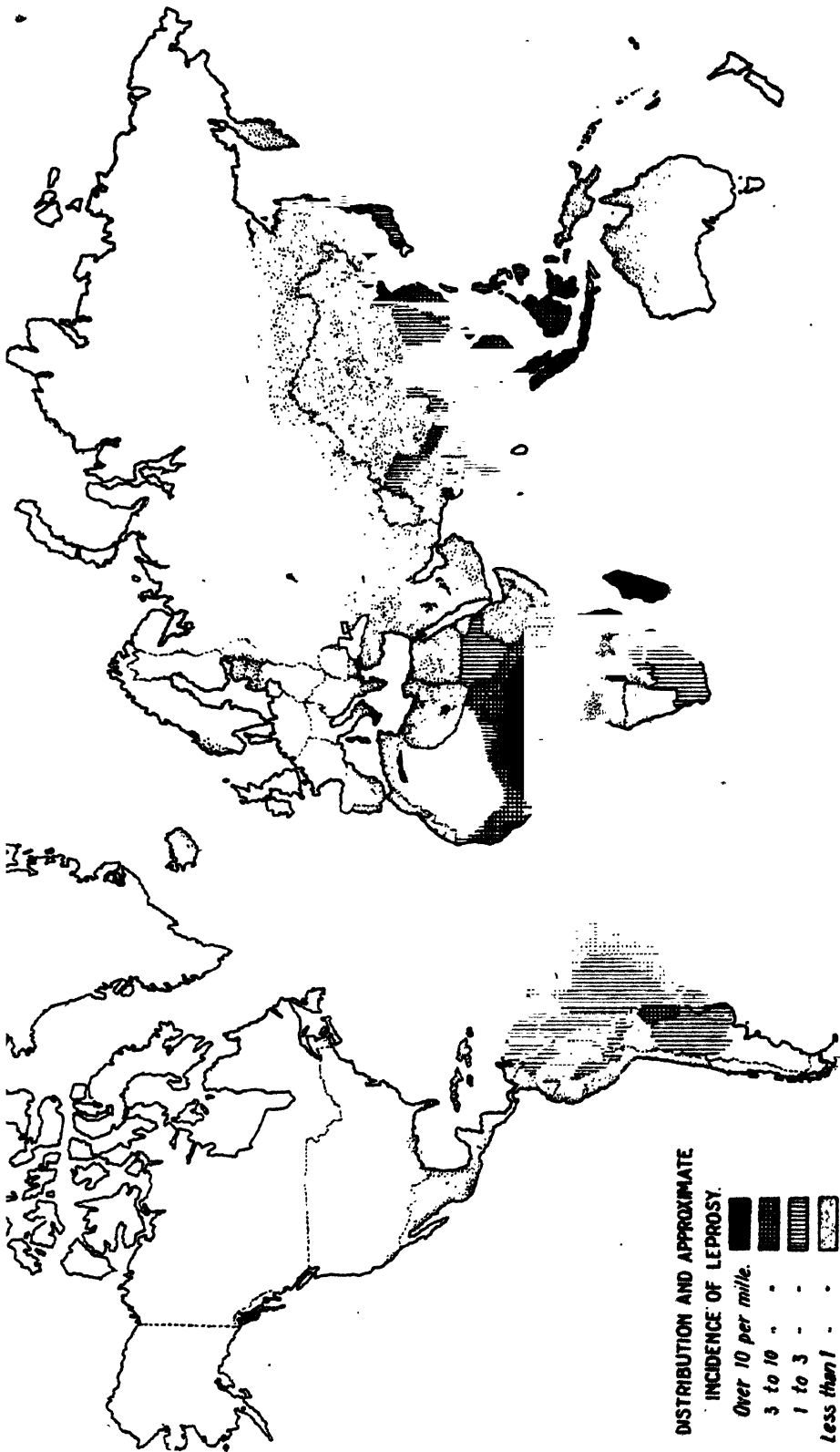
EPIDEMIOLOGY

Geographical distribution (*see map*).—The distribution and incidence of leprosy in different parts of the world is shown roughly in the map. Leprosy is now found chiefly but not entirely in the tropics. In the past,

leprosy was found commonly in temperate and even in very cold countries such as Iceland, but there is now little leprosy in such areas.

Leprosy is on the whole most common in areas where the climate is both warm and humid, and in hot dry climates the disease is often relatively rare or absent. The three great endemic areas are (a) Africa, particularly equatorial Africa, (b) a large part of Asia including India (particularly southern and eastern India), Burma, Siam, Indo-China and China (particularly the south), and (c) South America, particularly Brazil.





The incidence of leprosy in endemic areas and countries varies markedly. It is noticeable that, compared with some other chronic infective diseases, the incidence of leprosy is never very high. An incidence of more than 10 per cent of the population of an affected area is very rare, and when it has occurred it has been only temporary.

The varying incidence of leprosy in different parts of India and Burma is roughly shown in the map. The incidence for India as a whole is probably not more than 0.25 per cent. In Burma, Bengal, Orissà, Madras and other parts of southern and eastern India, most of these areas being low lying, hot and humid, the incidence of leprosy is generally high, 0.5 to 3 per cent, and may be 5 per cent or more in certain areas. In individual villages, the incidence may be 10 or 15 per cent or more. In some, if not most, of these highly endemic areas, many cases are mild. In central and western India, where the climate is hot and fairly dry, there is on the whole a low incidence, and in the north-west of India, where the climate is very dry and much more extreme, *i.e.* very hot in summer and cold in winter, there is very little leprosy. In the Himalayan foothills, however, even in the north-west of India, leprosy is relatively common.

In other endemic continents and sub-continents, for example, Africa and South America, similar marked variations in incidence are seen.

By **type-distribution** is meant the proportion of cases of leprosy belonging to the two main types, neural and lepromatous. Observations of the incidence and severity of leprosy have revealed the following interesting facts regarding the type-distribution of cases. In India, in areas where the incidence is high, most of the cases, usually 70 per cent and sometimes even 90 per cent or more, are of the neural type, often of the tuberculoid variety, and many are slight and abortive. In contrast with this, it is found that in other areas, and commonly where the incidence of leprosy is relatively low, the average case is often much more severe, and 50 per cent or even more may be of the lepromatous type. There are in India relatively few areas where leprosy is both common and severe. These few areas include part of the Madras Presidency and certain Himalayan hill areas.

In Africa, similar variations in type-distribution have been recorded, but they are possibly less marked, and in most areas the milder neural cases appear to predominate. In some other countries, including Burma, the Philippine Islands, Japan, South China and also South America, lepromatous cases appear to form a high proportion, often a much higher proportion than in India and in Africa.

Leprosy and age : Differences in susceptibility at different ages are shown by a study of leprosy in families. Adults long exposed to infection in families show an incidence averaging about 5 per cent, while children similarly exposed to infection may show an incidence of 50 per cent or more. These differences may not be entirely caused by the age factor. Other possible factors are mentioned elsewhere.

It is also suggested that, if leprosy is contracted early in life, it is more likely to take a serious form than if contracted later in life, but evidence on this point is not very clear.

The **incidence at different ages** has been studied in two ways. In a few areas it has been possible to study the actual incidence in different age-groups, but this involves a complete census of the population. More often practicable is a study of the age-distribution of the cases detected in surveys. Here three age-groups are considered : up to 15—the early age-group, 15 to 34—the middle age-group, and 34 and over—the late age-group; these age-groups being chosen because in India they are of approximately the same size, and because accurate ages may be unobtainable.

In most endemic areas, the largest number of cases, and sometimes the highest incidence, will be found in the middle age-group. This finding, however, does not indicate the age when the disease is acquired, for leprosy is a very chronic disease with a long latent period. Studies of the age of onset indicate that symptoms most commonly appear at the period a few years before and after puberty and, when the latent period is allowed for, it appears that most leprosy infections are contracted in childhood or early in adult life.

While the highest number of cases is generally found in the middle age-group, marked variations are found both in the relative incidence and in the proportion of cases in the early and late age-groups. The findings in this respect may vary in different countries and in different parts of the same country, and also may show some relation to the type-distribution which has already been discussed.

In areas in which the severer lepromatous forms of the disease are common, leprosy frequently shortens life, so that the number of cases and the incidence in the late age-group is relatively low. At the same time the infectiousness of the lepromatous cases is sometimes associated with a considerable incidence of leprosy in children and young people. In such circumstances a high proportion of the cases is found in the earlier age-group, and a low proportion in the late age-group.

Contrasting with this is the state of things found in areas where the mild neural type of the disease predominates. These mild forms of the disease do not appreciably shorten life, and the result is an increase in incidence with increase in age, and a high proportion of the cases in the late age-groups. Together with this, the low infectivity of most of the cases is often associated with a relatively low incidence in children.

There are of course areas in which the type-distribution and age-distribution of the cases, and the incidence in different age-groups, come midway between these two extremes, and also it must be admitted that sometimes rather anomalous findings are recorded, which are difficult to reconcile with the general ideas here expressed.

A study of **type-distribution at different ages** has given additional information of some interest. The findings vary markedly not only in different countries but sometimes in different parts of the same country. In some countries, including many parts of India, the proportion of frank lepromatous to neural cases in the early age-group is low, and shows a relatively small rise in the later age-groups. Such findings indicate that the disease is relatively mild and often not progressive.

In other areas, however, the proportion of frank lepromatous cases in children may be higher, and in the later age-groups lepromatous cases may be in the majority. Such findings indicate that, in these areas, the disease is relatively severe and progressive.

The importance of **type- and age-distribution of cases** is now being increasingly recognized, for crude incidence figures may give little indication of the public-health importance of leprosy in any area. A high incidence, if associated with mildness of the disease, as shown by the figures for type-distribution, and a low proportion of cases in young people, as shown by the figures for age-distribution, may be considerably less serious than a lower incidence of leprosy in its severer form, with the infection of numerous young people.

Sex incidence.—Studies of leprosy in the general population have shown that, in most parts of endemic countries, the incidence of leprosy is higher in men than in women, sometimes twice as high. A slight difference is found even in childhood, and the difference becomes more marked in adult life. Also females tend on the whole to show milder forms of the

disease. The reasons for these differences are not clear. The possible causes are an inherent lower susceptibility of females, or a less degree of exposure to infection.

The influence of heredity: Race.—There is considerable evidence to show that the severity and the forms of leprosy vary quite markedly in different countries, and it has been suggested that some races are more susceptible to leprosy than others. These suggestions have been borne out by studies of persons of different races in the same place, for example, Indians, Chinese, and Malaysians in Malaya, Indians and Burmans in Burma, Indians, Negroes, and others in the West Indies, and Europeans and Africans in Africa, reported by different workers. No matter where the case of leprosy is found, there is a marked tendency for the form of leprosy to be influenced by the race of the person affected. The differences in type-distribution of leprosy in different countries, which have already been mentioned, are possibly caused largely by these differences in racial immunity. It has been suggested that racial immunity may be gradually built up as the result of the long endemicity of leprosy in the particular race, and it has even further been suggested that the dying out of leprosy in Europe may have been partly or largely caused by the development of this immunity in European races. It is difficult however to correlate the degree of susceptibility to leprosy of a race with the length of the period of endemicity in that race. For example, the Chinese among whom leprosy has been endemic for many centuries appear relatively highly susceptible to leprosy.

Moreover, persons of the European races among whom leprosy died out a few hundred years ago may be more highly susceptible than many persons of other races in whom leprosy is still endemic. An Englishman in the tropics will very rarely get leprosy, but, when he does, he will often get it in a severe form. In the southern part of the United States, particularly Louisiana, the large Negro population, in spite of relatively poor hygienic conditions, shows a much lower incidence of leprosy than the population of European descent, especially French and German. These facts indicate that the postulated acquired immunity of European races, if it was ever a reality, may have died out since leprosy died out in Europe. At any rate, at the present time, Europeans often show relatively little immunity. Our knowledge of this subject, however, is very incomplete, but it is clear that race is of importance.

Familial susceptibility.—From ancient times it has been realized that leprosy often runs along certain familial lines, and this gave rise to the belief that leprosy was hereditary. This idea has been disproved. The possibility of susceptibility to leprosy being hereditary, however, has to be considered, and a suggestion has frequently been made that in certain families, certain persons exposed to infection develop the disease far more readily than persons of other families similarly exposed to infection, and this suggestion is supported by a certain amount of evidence. Accurate evidence on this matter, however, is very difficult to collect, and information so far available is not completely convincing. The evidence regarding a high susceptibility of certain races already mentioned does however point in this direction, for a race is simply a large group of families.

An interesting suggestion has been made that the rarity of marital infection, and the relative frequency of infection of children in families, may be influenced by the fact that the husband and wife are usually of different familial stock and are not blood relations, whereas the children are of course the blood relations of the leprous parents.

If susceptibility to leprosy were truly hereditary, it should be inherited according to Mendelian law, and there is also a remote possibility that 'somatic linkage' between this possibly hereditary factor and some other

easily recognizable hereditary factor might be found. As Weiner points out, this can only be done by studying three generations of affected families and, as far as is known, this has not been attempted.

The idea that leprosy is more common or more severe in persons of certain Landsteiner blood groups than in others has been suggested, but the author and others have failed to confirm this. The blood groups are of course entirely hereditary. The blood grouping of cases of leprosy of all types shows no significant difference from the blood grouping of healthy persons of the same population.

It will be seen that definite evidence regarding familial susceptibility to leprosy is scanty, but it is a matter of common experience that some persons may acquire leprosy from very slight contact for a very limited period, while other persons with long and intimate contact do not acquire the disease, and it is not impossible that these individual variations in susceptibility are related to family and heredity.

The influence of environment: Climate. A possible relationship between climate and leprosy has already been hinted at in the discussion on the distribution and incidence of leprosy. In the world as a whole, leprosy is most common in areas which are both warm and humid, and it appears that these conditions favour the transmission of the disease. High temperature, however, with a low humidity is often associated with a low incidence of leprosy, and therefore humidity appears to be of more importance than temperature. When leprosy is studied more in detail, however, certain facts are revealed which are not in accordance with these ideas. For example, in the very humid eastern part of Bengal, leprosy is considerably less common than in the drier western part of Bengal. Dry central Burma shows a higher incidence of leprosy than the more humid southern Burma.

It appears probable that climate is only one of a number of factors influencing the spread of leprosy. The fact that leprosy used to be common in temperate and cold climates indicates that a high temperature is not necessary for transmission, but the fact that infectious cases of leprosy imported into or repatriated to European countries, although often not isolated, very rarely give rise to secondary cases, indicates that, under modern conditions, transmission in temperate or cold countries rarely occurs.

In addition to the possible influence of climate on transmission, it appears that climate also has an influence on the progress of the disease; in spite of the fact that leprosy is mainly a disease of warm countries, it is the common experience that persons suffering from leprosy in cold and temperate climates often benefit physically by a removal to a warmer climate, provided that it is dry and bracing.

Diet.—There has been from ancient times a common idea that leprosy is influenced by diet, and even caused by diet. In different parts of the world, different items of diet have been blamed. Fish and meat are two items of diet often mentioned in this connection. The attempt of Sir Jonathan Hutchinson in the 1890s to explain the distribution epidemiology of leprosy by his 'fish eating' theory is now of historical interest only. During recent years, it has frequently been pointed out that, in Asia, the incidence of leprosy is highest in those areas where rice is grown and forms the staple diet, but nobody believes that the rice diet has any direct causative relationship with leprosy. The association of leprosy with rice areas may be caused more by climatic and racial factors than by the diet factor.

A lack of salt has been mentioned in connection with a high incidence of leprosy, as well as the consumption of the toxic foods. The idea has been advanced on very unsatisfactory evidence that the eating of *colocasia antiquorum*, which contains sapo-toxins, is an important predisposing cause of leprosy. This foodstuff under various names is commonly consumed

in many tropical areas, but the evidence to support this theory is of a very similar nature to, and, as completely unconvincing as, the evidence which Hutchinson quoted to support his 'fish eating' theory of the causation of leprosy.

Largely from analogy from other similar diseases such as tuberculosis, it appears possible that deficient diet in general rather than the consumption of some particular article of diet may influence the spread of leprosy in the community, and the development of the disease in the individual. This is by no means certain. The few diet surveys that have been made in relation to leprosy have given inconclusive results.

Social and hygienic conditions.—There is some evidence to show that social and hygienic conditions affect the incidence of leprosy, and that under good conditions the disease may tend to die out. In India and other countries, this factor may be of considerable importance, but the distribution and incidence of leprosy cannot be explained on this basis alone, since in very poor areas leprosy may be rare, while in neighbouring prosperous areas with better conditions, leprosy may be much more common. There is, however, no doubt that leprosy is to a considerable extent aggravated by bad social and hygienic conditions. Poverty, bad diet, poor housing with overcrowding, and ignorance of ordinary hygiene often go together, and favour the spread of leprosy. It is perhaps bad housing necessitating close and intimate contact of an infectious case of leprosy with healthy people in the home, which is of greatest importance. Among aboriginal and semi-aboriginal people living under very primitive conditions, leprosy is usually rare. Ancient tribal customs and traditions often include drastic precautions against the spread of leprosy, and the breaking down of these customs without the institution of other hygienic measures may cause leprosy to spread.

In some countries, including India, two special factors probably have an important bearing on leprosy. The first is the religious sentiment which regards leprosy as a divine visitation, which encourages those suffering from leprosy to go on religious pilgrimages, and which also fosters the giving of alms to beggars in general, and to those with leprosy in particular. The second is the joint family system under which a father, mother and all married sons and their families, and all unmarried sons and daughters share one household; this favours the spread of leprosy in a family if the infection is introduced.

Another factor, probably of increasing importance, is the industrialization now occurring in tropical countries where leprosy is common. Workers from the rural areas sometimes with little or no leprosy are migrating with their families in very large numbers to industrial centres, where they may get infected by workers with leprosy coming from other areas, and they may return to their villages and introduce the disease there. Housing and other conditions in industrial areas often favour the transmission of leprosy.

PATHOLOGY

The pathology of the two main types of leprosy is markedly different, and therefore the two types will be discussed separately.

Neural type: Morbid anatomy.—The changes seen in the skin are described under Symptomatology. The only other important changes are in the **peripheral nerves**. The affected nerve often shows marked thickening over large parts of its course, but there is frequently marked thickening of some parts, with thinner portions in between. The thickened nerve is often hard, the surface rough, and it may be adherent to surrounding tissues. On opening the nerve, the sheath is found thickened, and the nerve bundles, if

still recognizable, are often widely separated by whitish streaks of chronic inflammatory tissue. These tissues may have undergone caseation and, where the areas of caseation are large, nerve abscess may be formed. In chronic long-standing cases of the neural type, the nerve, instead of being thickened, may be thin and atrophic, and consist of little more than fibrous tissue.

In the areas supplied by affected nerves, **trophic lesions** will often be found in the form of decalcification, rarefaction and absorption of bones. The only other change worthy of note in neural cases is the slight enlargement of **lymphatic glands** sometimes seen in the neighbourhood of marked tuberculoid lesions.

Histopathology.—This varies widely according to the clinical variety of the lesions as described under Symptomatology. In the '*simple*' variety of lesion the changes take the form of cellular infiltration of the small round cell type, partly diffuse, partly peri-vascular and to some extent peri-neural. There is an absence of the changes described below as '*tuberculoid*' and '*lepromatous*'. In the writer's experience, clinically simple lesions often show slight tuberculoid histology, and occasionally early lepromatous changes.

In lesions of the '*tuberculoid*' variety, whether in the skin, the cutaneous nerve, or the nerve trunk, the characteristic histological appearance is very similar to that produced by infection of the tissues with tubercle bacilli, hence the term '*tuberculoid*'.

The lesions consist essentially of small foci of epithelioid cells, often surrounded by areas of round cell infiltration, and often in the centre showing Langhan's giant cells and occasionally necrosis. (It is this necrosis which causes the nerve abscess, and the ulceration of the skin patches occasionally seen.) The small foci frequently coalesce and form large masses. In these lesions, bacilli are usually relatively few, and may be very difficult to detect in smears or sections. For some reason which is not clear, in the neural type of leprosy there is a marked tendency for these lesions to appear in the terminal nerve branches in the skin, from whence the changes spread up the subcutaneous nerves, and frequently cause marked lesions in the nerve trunks. Hence the anæsthesia and nerve involvement in the neural type of leprosy.

In the neural type of leprosy, these changes are found only in certain sites, namely, in certain areas of skin, in cutaneous nerves and nerve trunks, and sometimes in lymph nodes. There is no similar involvement of the skin as a whole, or of the mucous membranes, internal organs, etc.

Lepromatous type : Morbid anatomy.—The changes in the skin are described under Symptomatology. In the active phases of the disease the skin is thickened, has lost its elasticity and has a greyish white colour on section. There are often thickening and infiltration in the **subcutaneous tissues**. Peripheral nerves may show thickening, usually of slight or moderate degree, over a considerable part of their course. There is frequently a slight generalized involvement of **lymph nodes** and **lymphatic vessels**. The alimentary tract is affected only at its upper end, with infiltration of the mucous membrane of the mouth and pharynx. The upper part of the **respiratory tract** is also affected in a similar way, and this affection may extend down into the bronchi and bronchioles, but there is no affection of the parenchyma of the lungs. There is frequently slight enlargement of the **liver** and **spleen** caused by a chronic interstitial infiltration, and these organs may show a slightly irregular surface and a mottled appearance on section. The **testes** often show chronic infiltration and enlargement, but may be atrophied. The **vascular system** shows little affection, the heart and larger vessels and the arteries usually being normal, but the veins in

the affected tissues often show slight chronic inflammatory changes. The central nervous system is not affected.

Histopathology.—Wherever the lepromatous lesions are found, their histopathology is roughly the same. The tissues show interstitial infiltration with inflammatory cells, the cells however being very different in character from those seen in lesions of the neural type. The epithelioid cells are few and Langhan's cells are absent. There is no marked tendency towards the involvement of nerve as compared with other tissues, most types of tissues being invaded. The characteristic cell is the histiocyte, in which the protoplasm frequently undergoes fatty change with the formation of vacuoles which may be filled with fatty material and masses of acid-fast bacilli ('foamy' cell of Virchow). In this type of lesion, bacilli are demonstrated in large numbers with great ease. Such lesions are found in the skin, the nerves, the mucous membranes, the lymphatic glands, the bone marrow, and the internal organs.

SYMPTOMATOLOGY

There is almost invariably a considerable **latent period** between the time when bacilli enter the body and the definite appearance of the signs of leprosy, but it is only in exceptional circumstances that the time of the transmission of infection can be fixed with any accuracy. In such cases, latent periods as short as a few weeks and as long as twenty years or more have been reported. Some books describe **prodromal symptoms** with malaise, fever, rigors and pains in various parts of the body as commonly occurring before definite signs of leprosy appear and before diagnosis becomes possible.

In the experience of the writer, and, he believes, of most other leprosy workers, such prodromal symptoms are very rare. Such symptoms are not common even some time after clear signs of leprosy are evident. Such reports suggest strongly that the diagnosis of the disease has been unnecessarily delayed until the disease has become generalized and 'reaction' has occurred.

The **onset** of the symptoms varies greatly. In countries such as India where most people are not highly susceptible, the onset is usually gradual, often very gradual; very commonly there is seen a single initial slowly spreading lesion with no general symptoms whatever. Some workers have regarded such initial lesions as the primary lesions at the site of the original infection. This seems doubtful, but the possibility of some initial lesions being primary cannot be ignored. In other patients, the lesions from the start are multiple. Several patches may appear in various parts of the body, and slowly spread. In other countries, and even in India in those persons who are more highly susceptible, the onset of the disease may be much more sudden, and there may be a rapid appearance of lesions in many parts of the body, sometimes with malaise, pain in the limbs, fever, etc.; cases with such an onset however are relatively few.

Types of leprosy.—Leprosy is usually a generalized or systematic infection, and the infection is rarely if ever confined entirely to one particular tissue (although in certain cases the recognizable lesions may be so confined). Clinically, however, leprosy shows itself in two main forms to which the term *neural* and *lepromatous* are now being applied. The definition of these two main types of leprosy adopted at the International Leprosy Congress, 1938, has already been given. The common clinical manifestations of these two main types are here described.

NEURAL TYPE

The lesions seen in cases of the neural type can be divided into two varieties for which the terms *macular** and *anæsthetic* may be used.

The *macular variety* (see plate XV).—There appear in the skin one or more patches usually clearly defined, round, oval, or irregular in shape, in which one or more of the following changes are found :—

- (a) Loss of pigment.
- (b) Diminution in cutaneous sensibility.
- (c) Thickening of the cutaneous nerve supply of the area.
- (d) Thickening and erythema, particularly at the margin, occasionally going on to ulceration.
- (e) Dryness due to impairment of sweat function, scaliness, failure of hair growth, etc.

The loss of pigment is usually not complete. It may be more marked in some parts of the patch than in others. It may be obscured by erythema, or, in countries such as India where such treatment is widely practised, by scarring caused by the application of caustics.

The diminution in cutaneous sensibility varies. It is usually slight in patches on the face, rather more marked in patches on the trunk, and most marked in patches on the limbs, while in individual patches the centre may be more affected than the margin. All sensations are not equally affected; the earliest sensory changes are often those affecting the sensation of heat and cold and pain; later, the sensation of light touch is affected. These sensory changes detectable by the physician are often accompanied by sensory changes described by the patient, such as feeling of hyperæsthesia, and formication, pain and tingling when the part is struck.

The thickening of cutaneous nerves supplying the macule may not be easy to detect, although sometimes it is marked, particularly in cases with marked thickening of the macules. Careful examination made with a knowledge of the distribution of cutaneous nerves will, however, not infrequently reveal nerve thickening, and this thickening may be traced from the patch up the cutaneous branches into the nerve trunks, which may also be thickened (see plate XVI, figures 1 and 2).

Thickening and erythema of the skin are often present in active macules, but they vary greatly in extent and degree. They may be very slight, and affect only the extreme margin; they may be more marked, and affect the whole outer zone of the patch; they may be very marked, and affect the whole patch, in which case they may be accompanied by scaling of the epidermis and occasionally by actual ulceration. Flat patches often become thick and red, and later become flat again. The thickening of patches may be very rough and uneven, and sometimes patches have a papillated appearance (see plate XV, figures 2, 3, and 4).

* The use of the term 'macule': In general dermatology, the term macule is used to signify a circumscribed lesion of the skin with pigmentary change but without elevation or depression. Leprosy workers, however, have for many years used the term to signify lesions in which there may be a considerable amount of elevation, and, since no other more suitable term has been suggested, we here use the word 'macule' in this second sense.

PLATE XV.—LEPROSY. NEURAL TYPE. 'MACULAR' LESIONS.

- Fig. 1.—'Simple' macule. Flat, pale, slightly anæsthetic patches in a child.
 Fig. 2.—'Minor tuberculoid' lesion on the back. Slight irregular thickening and erythema at the spreading margin. Definite loss of sensation.
 Fig. 3.—Major tuberculoid lesion. Marked irregular thickening and erythema of the whole outer zone of the patch. Patch completely insensitive.
 Fig. 4.—Major tuberculoid lesion on the back. The whole patch thick, rough red, and completely anæsthetic.

PLATE XV

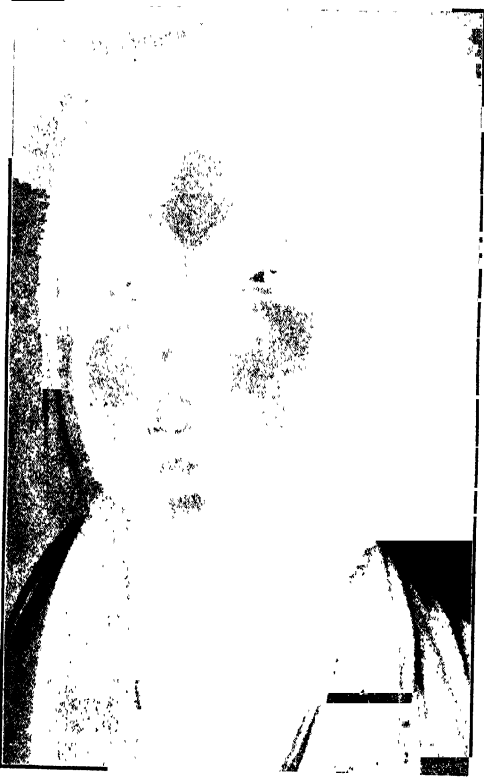


Fig. 1



Fig. 2

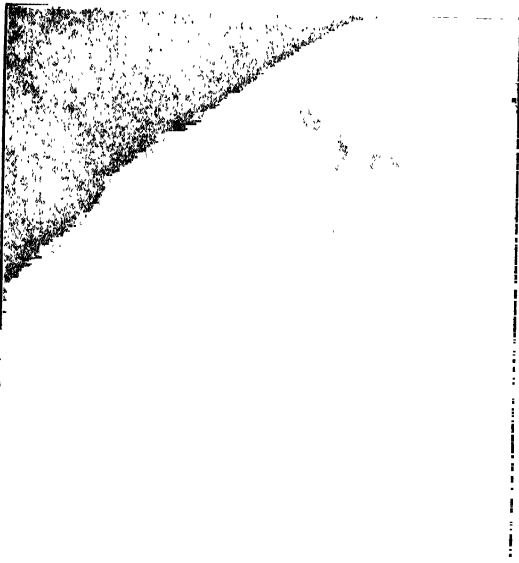


Fig. 3



Fig. 4



Fig. 1

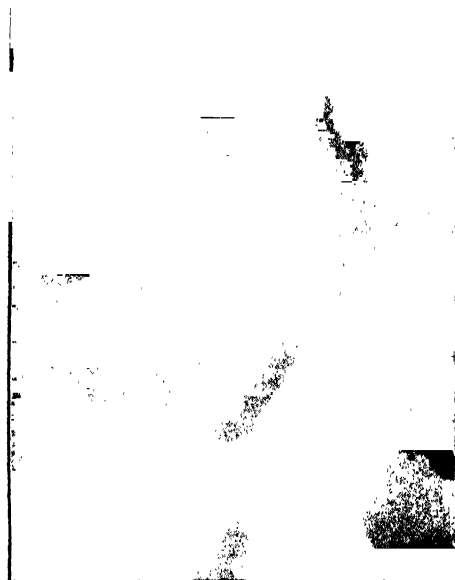


Fig. 2

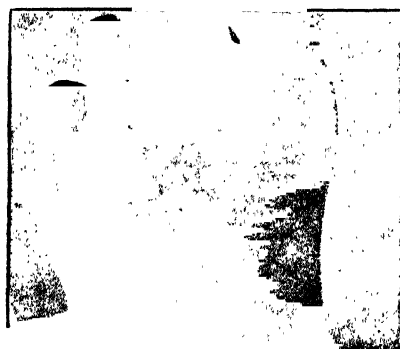


Fig. 4



Fig. 3



Sub-classification of macular lesions.—The International Congress on Leprosy, Cairo, 1938, suggested a sub-classification of cases of leprosy of the neural type on the basis of the nature of the macular lesions. The term *simple* is applied to those macules which are not, and show no evidence of having previously been, thickened, erythematous, and infiltrated. The *simple* variety of macular lesion is often associated with little or no nerve involvement. The term *tuberculoid* is applied to those patches which show definite thickening, erythema, and infiltration, or else show evidence (usually in the form of slight scarring and wrinkling) that they have previously been of this nature.

The degree of tuberculoid change in these patches may be indicated by the terms *minor tuberculoid*, *tuberculoid* and *major tuberculoid*. The tuberculoid variety of macular lesions is often associated with nerve involvement, which may be great. It should be emphasized that the different patches in the same patient are usually all of the same clinical variety.

This sub-classification is of considerable importance, because the different varieties of macular lesion are associated with differences in immunological, prognostic and pathological findings. This matter is discussed later.

Size, number, and spread of macules.—Macules of the types described above may be found anywhere in the body. They may be small ($\frac{1}{4}$ inch in diameter), or very large (a foot or more in diameter). There may be only one macule, there may be several or many macules, and in cases of reaction (*vide infra*) there may be hundreds of small macules, and, in such cases, the macules being thick, there may be a striking resemblance to a case of leprosy of the lepromatous type with nodule formation.

The active lesions show radial centrifugal spread, and this may cause coalescence of lesions. There may however be long periods of inactivity lasting for months, years, or for life.

Bacteriological examination of these lesions usually gives negative results, though sometimes a few bacilli are found, and occasionally (usually during temporary phases of reaction) bacilli are fairly numerous.

The anæsthetic variety.—This form of neural lesion is characterized by the occurrence of leprosy involvement of the peripheral nerve trunks. This may arise as the result of an ascending infection spreading up the cutaneous nerves supplying a macule to the corresponding main nerve, but it may also arise without any apparent involvement of the skin and cutaneous nerves. Certain symptoms appear in the distribution of the affected nerve or nerves. These may be enumerated as follows:—

(a) Impairment of cutaneous sensibility in the area supplied by the nerve starting peripherally and extending up the affected limb.

(b) Impairment of sweating, and consequent dryness and scaliness of skin in affected parts.

(c) Paresis or paralysis with wasting of muscles supplied by affected nerves, and consequent deformity.

(d) Trophic lesions, namely, decalcification and absorption of bones of hand and foot, and trophic ulcers, frequently with necrosis of underlying bone which may be extruded through the ulcer, commonly with secondary infection of trophic lesions.

Perhaps the commonest nerves to be affected are the ulnar nerve, the peroneal nerve, and the posterior tibial nerve.

PLATE XVI.—LEPROSY. NEURAL TYPE. NERVE INVOLVEMENT.

Fig. 1.—Thickening of cutaneous nerves supplying a patch on the forearm.

Fig. 2.—Thick branches of cervical plexus supplying patch around the ear.

Fig. 3.—Paralysis of 5th and 7th nerves. Anæsthesia of cornea and inability to close the eyes.

Fig. 4.—Trophic ulcers of foot caused by tibial nerve involvement.

Fig. 5.—Nerve abscesses of ulnar nerve exposed at operation. Two abscesses markedly thick nerve between are seen.

The affected nerve is usually thick, sometimes very thick, particularly the ulnar and peroneal nerves. Sometimes the involvement of nerves causes nerve abscess (*v.i.*, and see plate XVI, figure 5).

The lesion of the ulnar nerve is most marked above the elbow; this lesion produces anæsthesia of the little and ring fingers, and on the ulnar side of hand and forearm, and later paralysis of small muscles of the hand, with the development of the typical deformed 'claw hand' of ulnar paralysis. The peroneal nerve is often affected where it passes round the neck of the fibula. The result is anæsthesia of the dorsum of the foot and of the outer side of leg, and paresis of the peroneal muscles with the development of 'drop foot'. The posterior tibial nerve is commonly affected on the inner and posterior aspect of the ankle, and the result is anæsthesia and keratosis of the sole of the foot, and trophic ulcers (see plate XVI, figure 4).

Other nerves sometimes affected are the radial nerve, the median nerve, the fifth and seventh cranial nerves and the great auricular nerve. The involvement of the median and radial nerves causes anæsthesia of the hands, trophic lesions, and occasionally 'drop wrist'. Involvement of the fifth and seventh cranial nerves causes anæsthesia of the cornea, paresis of the orbital and facial muscles, ectropion, and lagophthalmos, with great liability to irritation of the eye by unfelt foreign bodies, conjunctivitis, corneal ulcer, etc. (see plate XVI, figure 3).

In marked cases of the neural type of the anæsthetic variety, there may be anæsthesia of all the limbs and of most of the trunk and face, and paralysis, trophic lesions, and deformities in the arms, legs, and face.

Bacteriological examination of the skin and nose in cases of the anæsthetic variety of the neural type usually shows no bacilli.

Nerve trunk involvement, its nature and significance.—Many patients have both nerve trunk involvement and skin patches which may be simple or tuberculoid, and the nature, significance and the course of the nerve trunk involvement are likely to be the same as those of these patches.

Some patients, however, have nerve trunk involvement only, and in the absence of patches it may be difficult or impossible to assess the nature and significance of the nerve trunk involvement. The more markedly thickened nerves, sometimes with nerve abscess, are usually 'major tuberculoid', and have a corresponding short course and a good prognosis. The period of activity will often be short, but much nerve damage may be done, and permanent disability caused. The less marked forms of nerve thickening are more likely to be of 'minor tuberculoid' or 'simple' nature, with less immediate damage but a greater tendency to chronicity and extension, and even to lepromatous development.

The neural type in general.—The chief clinical manifestations of the neural type of leprosy have been outlined. Both types of lesion, macular and anæsthetic, may be present in the same patient. For practical purposes, in cases of the neural type, we may regard the infection as being confined to the macules in the skin and to the affected cutaneous nerves and nerve

PLATE XVII.—LEPROSY. NEURAL TYPE. TUBERCULOID REACTION AND SPONTANEOUS SUBSIDENCE.

Fig. 1.—Marked inflammation and slight ulceration of tuberculoid lesion on face. *Lepra* bacilli fairly numerous in the discharge.

Fig. 2.—The same patient a few months later. Complete subsidence; no bacilli found. During the succeeding eight years, only very slight temporary lesions appeared elsewhere.

Fig. 3.—Marked general tuberculoid reaction.

Fig. 4.—Same patient about a year later. Subsidence was complete and permanent. (Eighteen years' observation.)

PLATE XVII



Fig. 1

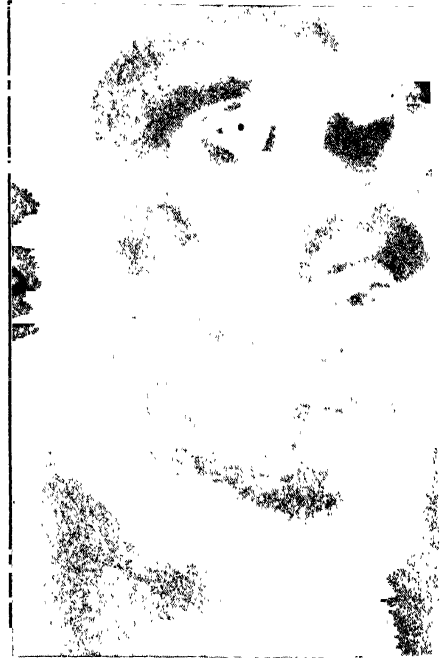


Fig. 2

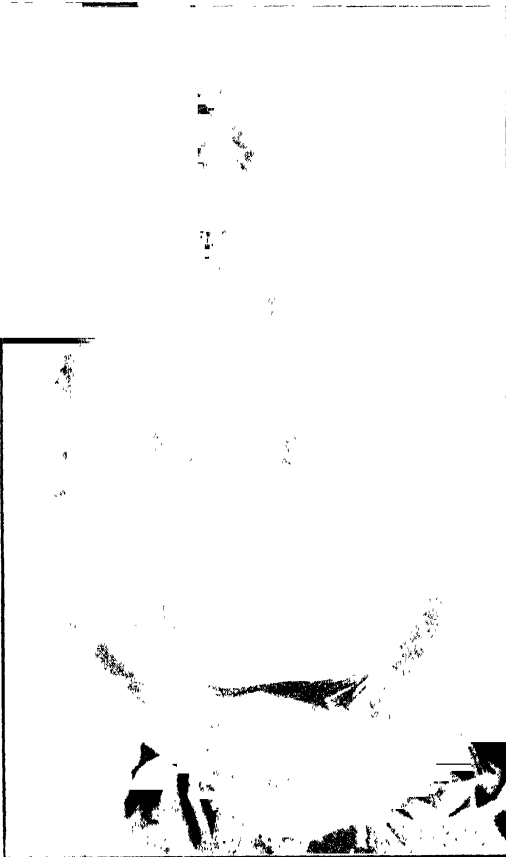


Fig. 3



Fig. 4

PLATE XVIII

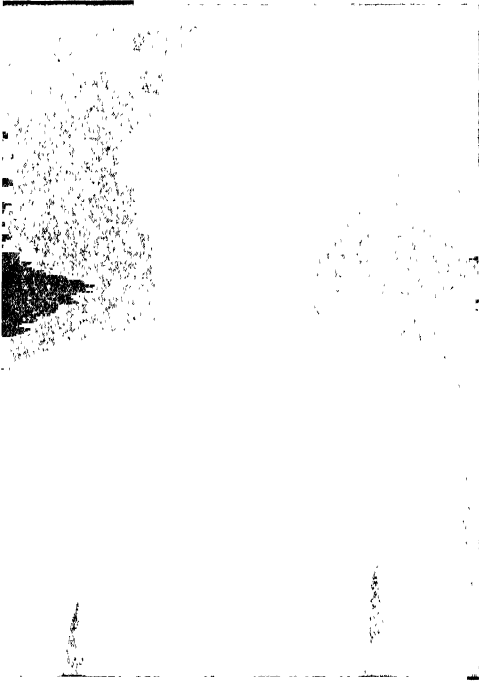


Fig. 1

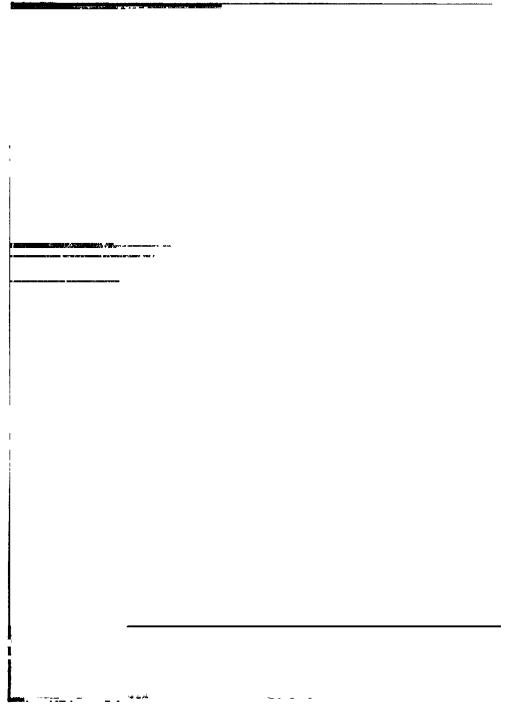


Fig. 2



Fig. 3

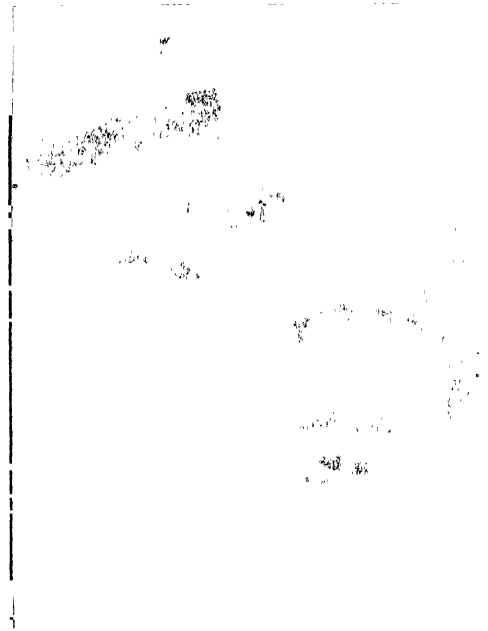


Fig. 4

trunks. There is as a rule no constitutional disturbance, except in cases with secondary infection or with reaction (*vide infra*).

Of all the symptoms described above, there are only two which are diagnostic of leprosy, namely, definite thickening of nerves and impairment of cutaneous sensation (*see* Diagnosis).

There remain to be discussed certain matters common to cases of the neural type in general.

Nerve abscess.—One curious feature of leprosy of the neural type seen in India, and particularly in Bengal, is the not infrequent occurrence of oval or circular swellings on leprosy nerves. The swellings may occur in cutaneous nerves, when they are usually small (the size of a pea), or in nerve trunks, when they may be much larger. The swellings are cold abscesses, which may burst into the surrounding tissues, and may discharge through the skin (*see* plate XVI, figure 5).

'Reaction' in neural cases. (*see* plate XVII, figures 1 to 4).—In some cases of leprosy of the neural type, there may be seen a phase of acute or sub-acute 'tuberculoid' activity of the lesions. To this condition the term reaction is applied. This reaction is probably of an allergic nature. It may occur naturally with no apparent cause; in some parts of India it is most commonly seen in the hot seasons of the year. It may be induced by the oral administration of potassium iodide, or by the administration of iodine in other forms, for in some cases of leprosy, iodine has the specific effect of inducing lepra reaction; reaction may also be induced by the injection of substances of an antigenic nature, such as tuberculin and lepromin and vaccines. Reaction may follow attacks of intercurrent disease such as malaria. Finally reaction is not uncommon in the puerperium in leprosy women.

The clinical manifestations of tuberculoid reaction are an acute or sub-acute inflammation of the lesions present, of the patches in the skin which occasionally ulcerate, and of the affected nerves which may show caseation. During reaction, new leprosy lesions may appear in the skin and nerves, sometimes in large numbers, or previously undetected lesions may be rendered easily detectable. At the beginning of the reactionary phase, there is often an increase in the number of bacilli detectable in smears taken from the lesions, and previously negative lesions may become positive.

The condition of reaction in neural cases is always a temporary one, and it subsides spontaneously, sometimes in a few weeks or months, but the reaction may cause severe damage to the nerves, with permanent disability and deformity. Reaction of the variety described in cases of the neural type, although its appearance may be alarming, is often not a bad prognostic sign, since it is frequently followed by long periods of inactivity of the disease, and it may be followed by permanent arrest of the disease. In a few cases however reaction may recur, even several times and at short intervals. The importance of recognizing reaction is emphasized later.

The course of the disease in the neural type.—The disease is localized to certain areas of skin and certain nerves, and as long as the disease remains in the neural form, this marked tendency to localization is maintained. In some cases, the number and the size of the lesions may show little or no increase over long periods, while in other cases, the size and number of the

PLATE XVIII.—LEPROSY. LEPROMATOUS TYPE.

Fig. 1.—Slight diffuse lepromatous infiltration of skin of face and body. Skin slightly thick, smooth, soft, and shiny.

Fig. 2.—More marked diffuse infiltration with tendency to nodulation on face and ears, with macules on the chest.

Fig. 3.—Marked generalized nodulation. (Such cases are rare in India.)

Fig. 4.—Lepromatous eye affection. Leprosy irido-cyclitis with hypopyon. Note lepromatous infiltration of face.

patches may increase steadily, and the number of nerves involved and the degree of involvement may also increase. This increase in the size and the number of lesions may be extremely gradual, or, in cases with reaction, it may be sudden and marked. In some cases, the extent and degree of skin involvement may show little or no increase, while the extent and degree of involvement of the nerves and nerve trunks supplying the affected areas may increase markedly, with resulting deformities, trophic lesions, etc.

There are some cases of the neural type which tend to develop into cases of the lepromatous type, but recent studies have shown that this change from neural to lepromatous type is relatively rare, and is largely confined to neural cases of the 'simple' variety.

The course of the disease in cases of the neural type varies markedly with the sub-type.

(i) *The course in neural cases of 'simple' sub-type.*—Such cases do not often remain indefinitely of this sub-type; a few lesions of this type may subside spontaneously. Some become lepromatous and follow a corresponding course as described later. Most of the others become tuberculoid, usually minor tuberculoid, and follow a corresponding course.

(ii) *The course in neural cases of minor tuberculoid sub-type.*—Minor tuberculoid cases are often characterized by extreme chronicity. There are some cases in which lesions remain localized and subside within a relatively short time, but in many cases the slight indolent activity goes on for years, with extension of the lesions of the margin and healing at the centre, with from time to time the development of new lesions, and also a tendency for increasing involvement of nerve trunks. Those cases of leprosy which gradually, over a period of many years, become crippled and deformed are frequently of this type. Sometimes a temporary phase of reaction with more marked tuberculoid activity will be seen, and this may be followed by quiescence and arrest, but is often followed by a resumption of the chronic minor tuberculoid activity.

Minor tuberculoid cases may remain mildly active for many years, sometimes up to thirty years or more. In such cases; apparent arrest even of long standing may be followed by renewed activity.

(iii) *The course of tuberculoid and major tuberculoid cases.*—In such cases, the skin lesions are clinically more marked and the degree of nerve involvement is also greater, as also is the tendency to tuberculoid reaction with positive bacteriological findings, but nevertheless the periods of activity of the lesions are often very much shorter, and may be limited to a few months or a year or two, while the tendency to extreme chronicity is much less marked.

In some cases, one or a few marked lesions may appear suddenly and spread for a short time, but this extension will soon stop, subsidence will occur, and the disease will often remain completely inactive for long periods and often permanently. Even very severe cases of generalized major tuberculoid reaction with numerous bacilli in the lesions, may subside permanently and completely, and the more marked the degree of tuberculoid activity, the greater is this tendency to subsidence.

Subsidence of marked tuberculoid activity is occasionally followed by minor tuberculoid activity of long duration, or after a considerable interval, by short periods of recurrence of major tuberculoid activity. This recurrence, however, is usually not repeated many times, and the disease commonly becomes quiescent and arrested. These phases of tuberculoid activity, however, may cause severe damage to nerves with permanent deformity.

(iv) *The signs of subsidence in neural cases.*—The patches, instead of being infiltrated and raised, become thinned and atrophic, and signs of fibrosis, in the form of wrinkling and scarring of the skin, are often seen.

Similar changes are found, but usually at a later period, in affected nerves, which, instead of being thickened and hard, become thin and fibrotic. As the result of this fibrosis, trophic changes often increase, and this increase must not be taken as indicating renewed activity of the disease.

LEPROMATOUS TYPE

As has been already mentioned in the definition of the two main types of leprosy, the lepromatous type of lesion is seen in cases of the severer 'malignant' form of the disease, in which there is little or no resistance to the infection, the bacilli multiplying and spreading in the tissues of the body

with little or no tissue reaction. The lesions are more diffuse in nature and more widespread throughout the body than in the neural type of leprosy, for the skin, nerves, mucous membranes, lymphatic glands and internal organs frequently show invasion. Clinically, however, the chief lesions are in the skin and in the mucous membranes.

The skin lesions (see plate XVIII, figures 1 to 4).—There is among medical men a common idea that this type of leprosy is characterized by the formation of nodules; this may possibly be true of leprosy in some other countries. In India, however, we find that nodule formation is relatively rare. The lesions of the lepromatous type of leprosy seen in the skin are, in order of frequency, as follows:—

1. Slight diffuse thickening, sometimes with erythema, the skin having a shiny appearance and giving a soft 'velvety' feeling on palpation.
2. Macules or circumscribed areas of skin with pigmentary change, differing from the macules of the neural type by having a smoother surface and an indefinite margin, by showing no sensory change or thickening of the cutaneous nerves, and by the fact that many bacilli are found on bacteriological examination.
3. Nodule formation in the skin or subcutaneous tissue, the nodules varying markedly in size and sometimes being so small as to resemble papules.
4. Ulcers caused by breaking down of nodules.

In cases of the lepromatous type, the lesions may, to begin with, appear to be localized in certain parts of the body, but this finding is often more apparent than real, for bacteriological examination of apparently unaffected skin in other parts of the body will frequently show bacilli, and, in severe cases of the lepromatous type, almost invariably the skin of the whole body is affected. Clinically, however, the lesions are much more noticeable in certain parts of the body than in others, particularly on the face and ears, the back, the buttocks, the knees, the elbows, and the dorsal aspect of the hands.

One of the manifestations of leprous infiltration of the skin is the loss of hair, which may be seen all over the body, but is most commonly seen on the face, affecting the brows, chin, and lips.

Other lesions of the lepromatous type.—In this type of leprosy, sensory change is usually absent in the skin lesions, although there may be some anæsthesia of the limbs caused by leprous involvement of the peripheral nerve trunks. The nerves are involved, but the nerve thickening is usually much less than in the 'neural' type of leprosy, and anæsthesia, trophic lesions, paralysis, etc., are consequently a less marked feature. It should be mentioned, however, that in cases of the lepromatous type in which the disease in the skin gradually dies out, the subsidence of skin lesions (shown by fibrosis, wrinkling and thinning of the affected skin) is very frequently accompanied by increase in anæsthesia, trophic lesions, etc., caused by fibrotic changes in the nerves, which accompany the process of healing.

In the lepromatous type of leprosy, the **mucous membranes** are very frequently affected, the mucous membrane of the nose, pharynx and larynx being infiltrated, and sometimes showing nodulation and ulceration. Such lesions in the nose may cause destruction of the nasal septum and falling in of the nose, and in the larynx may cause hoarseness, and dyspnoea. Symptoms of leprous infiltration are also frequently seen in the eye (see plate XVIII, figure 4), in the form of chronic leprous irido-cyclitis and leprous infiltration of the cornea. Leprous invasion of the testes is also common, and is sometimes accompanied by loss of hair on the body, enlargement of the mammary glands, and other changes caused by lack of internal secretion of the testes. The other internal organs, the liver, spleen, bone marrow, etc., frequently show leprous lesions on post-mortem examination, but clinical symptoms are usually absent.

Reaction in lepromatous cases.—Reaction in the neural cases has already been discussed. A condition somewhat similar is also seen in cases of the lepromatous type, but in such cases the allergic nature of the reaction is much less clear, the clinical manifestations of reaction are often very different, and the prognostic significance of the reaction is also different.

In lepromatous cases, the manifestations of the reaction often include thickening, erythema, and sometimes ulceration of the infiltrations and nodulations in the skin and mucous membranes; the appearance of new nodules and infiltrations, sometimes very numerous and extensive, in the skin and subcutaneous tissues; and increase in the symptoms caused by leprous involvement of the mucous membranes, particularly of the nose and of the larynx (sometimes with epistaxis and blockage of nose, or dyspnoea caused by blockage of the larynx), and acute or sub-acute leprous irido-cyclitis. These clinical manifestations are frequently accompanied by constitutional disturbance, fever, rigors, prostration, etc.

Reaction in lepromatous cases may be very severe, and not infrequently lasts for a considerable time, weeks, or months, and when it finally does subside, the patient's condition is often worse than it was before the reaction. Also the reaction is apt to recur periodically, with a progressive deterioration in the patient's condition. Such reaction, however, even if very severe, rarely causes death, though death from intercurrent disease during or after the reaction is not uncommon. The importance of recognizing reaction is emphasized later.

The course of lepromatous cases.—The course of the lepromatous cases is very different from that of the neural cases. The disease to begin with may be localized to certain limited areas of skin, and there are a few cases in which, after a limited period of localized activity, the disease subsides, but in the majority of cases the disease gradually progresses, the lesions become more marked and more widespread, and, finally, generalized.

This process may be relatively rapid, taking only a few months, or it may be much slower and take several years. The process of generalization may be accelerated and made more obvious by the occurrence of reaction, and, in severe rapidly progressing cases, these reactions may occur repeatedly at short intervals, and the general condition of the patient may rapidly deteriorate. In such cases, death from intercurrent disease and weakness is not uncommon, and the whole course of the disease may be only a few years. Even in such cases, however, if the patient can be tided over the period of intense activity, sooner or later subsidence and arrest of the disease may be seen, such subsidence, however, being sometimes accompanied by marked disability, deformity, permanent eye affection, etc.

In other cases, however, the disease is much more chronic, and this is seen particularly in patients in whom the infiltrations and nodules are hard and fibrous, although often prominent. In such cases, reaction may be entirely absent, and there may be long periods during which clinical activity and any extension of the lesions may be very limited if not entirely absent. The increase of the disease may be very slow, and subsidence when it begins may be correspondingly slow. In such cases, though the course of the disease of the lepromatous type may be very prolonged, twenty years or more, subsidence may leave the patient relatively little disabled and deformed.

Thus two varieties of lepromatous cases have been described, one being acute and rapid, and the other being of great chronicity. Between these two extremes come most cases of the lepromatous type. The disease is serious and may shorten life considerably, but subsidence with a greater or less degree of deformity and disability is not uncommon, and the prognosis of lepromatous cases, though grave, is not so hopeless as is sometimes stated.

Signs of subsidence in lepromatous cases.—These are the gradual disappearance of inflammatory changes in the lesions, shrinkage of the lesions with a diminution and final disappearance of the bacilli in them, the skin being left in a shrunk or shrivelled and flaccid condition, and often pendulous. Similar changes are seen in the lesions in the mucous membranes and in the nerves, and the fibrosis of nerves is frequently accompanied by actual increase in the trophic changes, which should not be taken as indicating activity of the disease itself.

CASES OF DOUBTFUL CLASSIFICATION

While nine cases out of ten, or even nineteen out of twenty, can be classified as neural or lepromatous on clinical grounds with reasonable accuracy, there are cases in which this is difficult or impossible, because the lesions are not entirely characteristic of either type, and show some of the features of both.

There may, for example, be infiltrated patches with anæsthesia and some nerve involvement, but the patches may be smooth, have an indefinite margin and show numerous bacilli in smears. Less commonly some of the lesions may be localized and appear to be neural, while other lesions may be more diffuse and appear to be lepromatous.

Bacteriological examination may be of little value in classification of such cases, since neural cases in the phase of reaction may show bacilli in considerable number. A very large number of bacilli in smears, however, does suggest the classification of the case as lepromatous.

Histological examination will, in some doubtful cases, make classification possible, but often clinically atypical cases will show atypical histology, and both tuberculoid and lepromatous elements may be seen in sections.

The lepromin test is of some value in classification and prognosis of such doubtful cases, a positive result indicating the probable neural nature of the case, with a correspondingly better prognosis.

In some of these cases the atypical clinical and histological findings are temporary, often associated with a phase of reaction. In a few weeks or months the case may become more typical, either neural or lepromatous, with corresponding clinical and histological findings and prognosis.

There is, however, a small number of cases in which clinical and other abnormalities persist, possibly for years, and accurate classification and prognosis are impossible.

THE DISEASE IN GENERAL

The relation between the two main types.—The idea that the neural and lepromatous forms of the disease may be caused by different strains of the organism is discussed and criticized elsewhere.

The idea has sometimes been expressed that the neural and lepromatous forms of the disease are merely early and late phases of leprosy, but that this is usually not so is now generally recognized. In many patients, the disease starts in the neural form and remains in the neural form throughout. In other patients, the disease starts in lepromatous form and remains in the lepromatous form throughout. The two main types of leprosy are apparently clinical manifestations of two widely different ways in which the body may react to leprosy infection. Those persons in whom there is some degree of immunity usually show the neural form, while those in whom there is little or no immunity show a much greater tendency to develop the lepromatous form.

It is true that there are some cases of leprosy which are not characteristic of either of these two main types, and which show some features of both, but these cases are, as a rule, not numerous. It is also true that there are

some cases of leprosy of the neural type which later develop into cases of lepromatous type, but it is believed that these are not numerous and that they mostly belong to the sub-variety of the neural type which has been called 'simple'. The classification of cases of leprosy is not merely of academic interest, since it has important bearings on prognosis and treatment, and also on preventive work, since the lepromatous cases are the infectious cases.

The wide differences in the clinical manifestations of the two main types of leprosy, and the less marked but the still definite differences between the different varieties of the neural type of lesion, have been outlined. The clinical differences are associated with differences in bacteriological findings, immunological findings, histological findings, course and prognosis. This relationship is outlined in the following table :—

TABLE

<i>Findings</i>	NEURO-MACULAR			Lepromatous
	Simple	Tuberculoid	Tuberculoid major	
<i>Clinical</i>	Patches flat and smooth. Nerve thickening, slight anæsthesia sometimes not marked.	Margins of patch show thickening, roughness, often papillation. Anæsthesia definite. Nerves often moderately thick.	Thickening of patch marked and not confined to margin. Anæsthesia marked. Nerve thickening often marked.	Skin lesions smooth ill-defined, usually infiltrated, may be nodular. Mucous membranes, etc., affected. Anæsthesia often found in limbs, but not in skin lesions.
<i>Bacteriological.</i>	Usually negative	Rarely positive	Usually negative, may be positive in 'reaction'.	Always positive.
<i>Lepromin test.</i>	Negative or weak positive.	Rarely negative, usually weak or moderately positive.	Practically always positive, usually moderate or strong positive.	Nearly always negative.
<i>Histo-pathology.</i>	Cellular infiltration, not 'tuberculoid'.	Definitely tuberculoid infiltration, but of moderate degree.	Markedly tuberculoid infiltration, sometimes caseation.	Foamy cell leproma. No tuberculoid structure.
<i>Prognosis and course.</i>	Doubtful. May become lepromatous, may become tuberculoid, or may subside.	Disease sometimes chronic and progressive to some extent. Rarely becomes lepromatous, subsidence fairly common.	Activity of disease often limited. Complete subsidence often seen. Very rarely becomes lepromatous.	Disease is usually progressive and becomes generalized. Subsidence rarely seen early, more often late after long period of activity. Relapse common.

Reaction.—There are certain points which have already been mentioned but of which further discussion is advisable. The first is the occurrence, in both of the main types of leprosy, of the acute or sub-acute condition which has been called 'reaction'. The failure to recognize this

condition and the fact that it usually subsides, sometimes in a relatively short time, even without any special treatment, has been a frequent cause of misunderstanding regarding the disease itself and the value of treatment.

The onset of reaction frequently brings the patient to the doctor, and the rapid subsidence of reaction often seen on the institution of treatment in such patients should not be attributed to that treatment. This mistake has often been made, and this fact helps to explain some of the 'rapid cures' of leprosy which have been reported from time to time. Many of the photographs showing patients before and after treatment, which have been published in textbooks and articles, are really photographs of lepra reaction and natural subsidence (*see* plate XVII, figures 1, 2, 3, and 4).

Ulceration in leprosy.—In both the main types of leprosy, ulcers may be seen, and there is a tendency to regard ulceration as indicating that patients are infective. The ulcers seen in cases of the neural type are of a trophic nature, caused frequently by trauma in tissues the vitality of which has been impaired by the destruction of the nerve supply including the vaso-motor fibres. These ulcers are usually seen in the feet or hands, and usually discharge no bacilli. In the lepromatous type of leprosy however, ulceration is also seen, most commonly in the nasal mucous membrane and less commonly in the skin lesions. These ulcers discharge very large numbers of bacilli.

Eye lesions of leprosy.—In both types of leprosy, lesions of the eye are seen. In cases of the neural type the lesions are caused by the destruction of the nerve supply, the fifth and seventh nerves. There is no actual leprous infiltration of the eye although there is frequently secondary (non-leprous) infection. In the lepromatous type of leprosy, however, the eye affections are caused by actual leprous infiltration of the eye, both superficial and deep (*see* plate XVIII, figure 4).

DIAGNOSIS

By a wrong diagnosis of leprosy, very grave injustice may be done, since the social consequences of a diagnosis of leprosy are often extremely serious. Without adequate grounds, a diagnosis of leprosy should never be made, and in doubtful cases, patients should be kept under observation until signs either disappear or become more definite.

Cardinal signs of leprosy.—It cannot be too strongly emphasized that there are only three diagnostic signs of leprosy, namely, impairment of skin sensation, thickening of nerves, and the finding of acid-fast bacilli. An excellent rule is 'Never diagnose leprosy unless at least one of these three signs is present'. Very occasionally one may have to depart from this rule, but only in very special circumstances (*see* p. 509). Generally one may say that, even if a case appears exactly like one of leprosy, unless one of these three signs is definitely present, the diagnosis of leprosy should not be made.

In diagnosis, thorough clinical examination is of the utmost importance. The whole body area should be examined in a good light for areas of loss of pigment, or of infiltration, which may be very slight. Palpation for thickened nerves should be carried out, and the skin sensation of the whole body should be tested. In doubtful cases, bacteriological examination of suspected areas of the skin may be needed in diagnosis, but such cases are few.

Testing for loss of sensation.—Loss of sensation is usually found either in the macules or else in the distal part of the limbs. The loss of sensation is usually partial and not complete, and may be very definite in some lesions and only very slight in other lesions. The most useful way to test for loss of sensation is to test the sensation of light touch. The patient's eyes are shut or bandaged, the skin is touched with a piece of paper or a feather, and the patient is asked to indicate with a finger the place touched. Failure to respond indicates impairment. Sometimes, particularly in patches on the face, touch sensation is retained

while the sensations of pain and of heat and cold are lost. The sensation of pain may be tested by means of pin pricks in the suspected area and in normal skin, the patient being asked to say which he feels most. In doubtful cases the heat and cold sensation may be tested.

Patience and care are necessary in testing sensation, and allowance must sometimes be made for the patient's mental condition, which may be dull. It should also be remembered that the skin sensation is normally dull in certain parts of the body, for example, over the elbows and in areas of hard thick skin.

The detection of nerve thickening.—Here a word of warning is necessary. A nerve is not thick merely because it can be felt. Many normal nerves (e.g. the ulnar, posterior tibial, peroneal and sometimes the great auricular) are palpable and give pain on pressure. A nerve should only be stated to be thick when it is definitely more thick than the same nerve on the other side of the body or, if both sides are affected, thicker than the same nerve in a person of similar build. Examination for thickened nerves should include palpation of the ulnar above the elbow, the great auricular, the peroneal, and superficial peroneal nerves, and also palpation of the subcutaneous tissue around and proximal to macules, for thickened cutaneous nerves.

The demonstration of acid-fast bacilli.—As has been stated above, this is not often necessary for diagnosis, but more often for judging whether a patient is infectious or not.

Sites of examination.—There is a common idea that the best way to demonstrate bacilli is to examine smears taken from the nasal mucous membrane. This is not so. Bacilli are much more commonly found in the skin. Nasal examination may be necessary in order to judge whether a patient is highly infectious or not, but it should be done in addition to, and not instead of, examination of the skin.

Bacilli are rarely found in anæsthetic areas or in macules of the neural type, though there may be a few found in the erythematous margins of such macules. Bacilli are found in the lesions which have been described above as lepromatous, i.e. areas of slight diffuse infiltration, thickening, nodule formation, etc. In cases of the lepromatous type, bacilli are very frequently found in the skin of the lobe of the ear, sometimes even in the absence of clearly visible lesions.

Methods of making smears.—The most generally useful method of examining the skin is known as the 'slit' method. Take up a fold of the suspected skin between the thumb and forefinger of the left hand, maintaining pressure to prevent bleeding, and with a sharp scalpel held in the right hand, make a slit vertically downwards into the corium. Still maintaining the finger pressure, with the point of the scalpel scrape the bottom and sides of the slit, collecting material on the point of the scalpel. Tissue cells, not blood are required. If there is excess of bleeding, wipe away the blood before scraping. Make a smear of the scraping on a slide, fix by heat, stain, and examine.

In nasal examination, inspect the nasal septum for lesions; take a suitable instrument and scrape away cells, not blood or mucus, from the lesion if visible, or from the septum near the anterior end of the inferior turbinate bone; make a smear on a slide, fix and stain.

It is most important that the slides and instruments used in making bacteriological examinations should be clean and free from acid-fast bacilli. This means that old slides should be used only after very thorough cleansing, and that instruments must be very thoroughly cleaned and sterilized between each examination.

Staining and examination of smears.—The method of staining used is that of Ziehl Neelsen which is described in many textbooks. The most important thing is that the stain shall be properly made, the basic fuchsin being ground in a mortar with a pestle to get proper solution in the absolute alcohol. It is not necessary to heat the slide in order to stain the bacilli, for if the stain is properly made, the bacilli will be stained in the cold in about twenty minutes. Watery acid or acid-alcohol may be used for decolorization, which should not be carried too far, and which should leave the film still slightly pink on washing with water. For counter-stain a strong watery solution of methylene blue is best.

When examining a slide, it is important to remember that other things besides bacilli may appear red; certain granules in some cells, fragments of horny epidermis, deposited stain may all be mistaken for acid-fast bacilli. The bacilli are characteristic in size and colour, and there should be no doubt about the genuineness of the bacilli seen. A safe rule is, 'If there is doubt, it is not a bacillus'. Bacilli, if present, are usually fairly numerous, often very numerous. If

only one or two bacilli are found in a whole smear, it is advisable to repeat the examination in order to verify the finding.

Cases with no cardinal signs.—It has been stated that, if none of the three cardinal signs is found, a diagnosis is very rarely justifiable. The most important exception is met in cases of leprosy in children. In young children who have been in close contact with an infectious case, one often finds on the face, body, buttocks or limbs, depigmented patches in which there are no sensory changes, no bacilli, and no thickening of nerves. In such cases, if the patch is typical in appearance and in site, a diagnosis of leprosy may be justifiable, but only when there is a history of close contact with an infectious case. It should be remembered that many other diseases (the chief of which is tinea) may cause apparent depigmentation of skin in children.

Miscellaneous points.—A mere diagnosis of leprosy is often of very limited value; the diagnosis frequently needs to be supplemented by notes as to whether the disease is of the neural or of the lepromatous type, whether the disease is active or inactive, and whether the case is an 'open' or 'closed' one. In determining these points, an accurate history and careful clinical examination and, in some cases, bacteriological examination are needed.

DIFFERENTIAL DIAGNOSIS

Three groups of diseases may be mistaken for leprosy.

Diseases which produce lesions in the skin which may resemble leprosy.—These may be enumerated as follows: Secondary and tertiary syphilide, tinea, leucoderma, leishmania infections of the skin (dermal leishmaniasis and oriental sore), psoriasis, yaws, lichen planus, erythema nodosum, dermatitis (sometimes occupational). Confusion may also occur between leprosy with reaction and acute inflammatory conditions of the skin such as erysipelas and cellulitis. Tertiary syphilide may closely resemble a macule of the neural type of leprosy. Dermal leishmaniasis (a post-kala-azar condition found commonly in Bengal, Bihar, Assam and Madras) often produces depigmented patches, infiltrations and nodules, which very closely resemble those of leprosy. Psoriasis with marked scaling of the lesions may produce an apparent but not real loss of skin sensation. Leucoderma produces marked depigmentation with no loss of sensation. The absence of the three cardinal signs of leprosy mentioned above distinguishes all these conditions from leprosy.

Diseases causing loss of cutaneous sensibility.—Many diseases of the central nervous system or of the peripheral nerves may cause some loss of skin sensation. Neuritis may be caused by toxins or by vitamin deficiency. Bernhardt's disease (neuritis of the lateral femoral cutaneous nerve), lead poisoning, polyneuritis (beri-beri), cervical rib, syringomyelia, traumatic injury to nerves, and diseases of the spinal cord, may all produce some loss of sensation in the limbs. Numbness of the limbs may also be produced by interference with the blood supply in conditions such as Raynaud's disease and obliterative endarteritis.

Most of these conditions are rare, some of them very rare. In countries in which leprosy is common, a case of leprosy is frequently wrongly diagnosed as one of these rare diseases mentioned. In most of these conditions, the distribution of the sensory change is not like that of leprosy, and there is no thickening of the nerves as would be expected in leprosy. In most of the nervous diseases mentioned above, the motor changes are more marked than the sensory changes; the reverse is usual in leprosy.

Conditions causing deformities and other lesions resembling the trophic lesions of leprosy.—These include such conditions as the trophic ulcer of the foot and gangrene seen in diabetes, the necrosis and gangrene of

the hands and feet, sometimes seen in Raynaud's disease and obliterative endarteritis, the deformities of tertiary yaws, deformities produced by trauma to nerves, involvement of nerves in callus formation after fractures, etc.

Multiple infections.—One point should be mentioned in conclusion. Not infrequently patients are found suffering from more than one condition of the skin, one of which may be leprosy. The commonest example of this is the combination of leprosy and tinea, for in India many persons, including patients with leprosy, also suffer from tinea versicolor. Other combinations of diseases that are not infrequently found are leprosy and syphilide, and leprosy and dermal leishmaniasis.

PROGNOSIS

The course of leprosy in its various clinical forms has already been discussed, and it has been seen how greatly this course varies. The statement sometimes made that leprosy is always or almost always progressive and sooner or later fatal is therefore seen to be extremely misleading, especially in view of the fact that in most countries where leprosy is common, the neural cases form at least 50 per cent of the cases seen, while in some highly endemic countries such as India and Africa, the proportion of neural cases may vary between 70 and 90 per cent or more, and a high proportion of these is commonly of the tuberculoid sub-type.

It appears desirable to outline what is meant by a good or a bad prognosis in a disease such as leprosy. Leprosy does not affect the vital organs and, in the absence of secondary infection, rarely causes death. Therefore the prognosis is concerned largely with the likely duration and severity of the symptoms caused by leprosy. A good prognosis in leprosy means that the disease will probably increase little, if at all, and will become inactive after a relatively limited period, although there may remain areas of loss of sensation and possibly deformities. By a bad prognosis we mean that the disease will remain active for a very much longer time, probably for many years; that during this time there is a possibility, or in highly susceptible persons a probability, of death from weakness or intercurrent disease; and that, if and when the disease does finally subside, there will probably be much more marked disability and deformity.

In prognosis the two chief factors to be considered are the type and sub-type of the disease and the race of the person affected. These two factors are often inter-related since in certain races the lepromatous type predominates, whereas in other races the neural type predominates.

In the neural type of leprosy the prognosis is, on the whole, good, but as already indicated, the nature of the lesions has a bearing on prognosis. If the lesions are of the tuberculoid variety in its more marked forms, the prognosis is usually excellent, whereas the presence of the kind of lesion which has been called 'simple' indicates an uncertain prognosis, since in such cases the disease not infrequently develops later into the lepromatous form.

In the lepromatous type of leprosy the prognosis is definitely poor.

As already stated the race of the affected person markedly influences prognosis. Many people of Indian and African races show leprosy in a mild and non-progressive form. In Europeans, and in persons of mixed European and other descent, the disease is much more often severe and progressive, and the same is also true of persons of some other racial groups, e.g. Chinese, Burmese, etc.

In addition to the type of the disease and the race of the affected person, the immunological reaction of the affected patient may influence prognosis.

The lepromin test, if positive, is a definite indication of a relatively good prognosis.

Another factor possibly influencing prognosis is the age at which the disease appears, since children and young people often show relatively little resistance to leprosy, but even in children the definitely tuberculoid lesions have a good prognosis.

The general physical condition of the affected patients and the presence or absence of intercurrent disease have frequently been quoted as having an important bearing on prognosis, but it is believed that their importance can easily be exaggerated.

TREATMENT

Introduction.—From ancient times until recently, leprosy has been regarded as a disease for which treatment was of very limited value. Hundreds of different remedies are mentioned in ancient and more recent literature, but the only one widely and persistently used and recommended has been the chaulmoogra group of oils. The history of this treatment is discussed later, and also some notes are given on other forms of treatment advocated in the past and occasionally used now.

During the last thirty years published reports on the value of treatment of leprosy vary markedly. Some writers have reported strikingly beneficial results from various forms of treatment; some of these reports have probably been based on the treatment of cases of the tuberculoid type, probably in the phase of reaction, cases which often show marked clinical improvement even without any treatment. Other writers have reported that treatment is of little or no use; some of these reports are probably based on the treatment of unsuitable patients.

The true position of leprosy treatment is considered to be between these two extremes, and it is the general opinion of experienced workers that, provided that patients suitable for treatment are selected, treatment is of definite value, but that beneficial results cannot be rapidly produced.

Selection of cases suitable for treatment.—Cases suitable for treatment belong to two main groups; firstly, cases of the neural type in which the disease is definitely active; secondly, cases of the lepromatous type which are not too advanced. The marked, chronic, and often inactive cases of leprosy of the neural type, with deformities, ulceration, etc., obtain little or no benefit from treatment. The severe or advanced cases of lepromatous type are frequently difficult or impossible to treat, because of frequent reactions and other complications.

General treatment.—This is of some importance. The elimination of intercurrent disease, such as syphilis, hookworm, malaria, and amœbiasis, may be necessary. Diet and healthy regime with regular hours, sufficient exercise, and sufficient rest are other matters of importance.

Special treatment with hydnocarpus preparations.—The term 'special' treatment used here does not signify 'specific', for it is not believed that there is any remedy for leprosy which is specific in the sense that quinine may be specific for malaria, arsenic for syphilis, antimony for kala-azar or the sulphonamide drugs in certain other diseases. Many different forms of treatment have been advocated and are still advocated in leprosy. This is an indication that no one form of treatment is entirely satisfactory. It is, however, the general opinion of experienced workers that the best form of treatment at present available is the administration of some preparation of hydnocarpus oil preferably by injection.

Historical.—The use of the chaulmoogra group of oils in the treatment of leprosy apparently originated in India at least 2,500 years ago for it is described

in the *Sushruta Samhita* of about that period. It has recently been pointed out that these writings indicate clearly the use of the oil of *Hydnocarpus wightiana*, but later this appears to have been replaced by other oils of the chaulmoogra group, and it is only in recent years that the use of the oil of *Hydnocarpus wightiana* has been resumed in countries, such as India, where it is readily available.

The use of the chaulmoogra group of oils in the treatment of leprosy spread early from India to other countries, and it was mentioned in Chinese literature many centuries ago.

In the nineteenth century, European physicians in India found this oil being used by practitioners of Indian medicine, and began to take an interest in it. The oil was administered by the mouth and by inunction, and various workers in India and other countries tried this form of treatment, some reporting some benefit, and others little or none. From 1879 onwards various chemists studied the chaulmoogra oils, isolated their fatty acids and prepared their salts, and these also were administered by mouth to patients with leprosy. The ethyl esters of chaulmoogra oil were first prepared in 1904 and marketed in 1907.

Injection treatment of leprosy was instituted in 1894 in Egypt where chaulmoogra oil was injected. Later, other workers injected various forms of the oil and also its ethyl esters and the salts of the fatty acids. The use of these preparations was confined to certain centres until about 1920. The excellent results of treatment reported by workers particularly in Hawaii and in India, encouraged the adoption of various forms of this treatment in most countries of the world, and, in spite of its limitations which are widely recognized, it is now the standard treatment in most countries.

Preparations.—The two preparations in common use are hydnocarpus oil (usually *wightiana*, but sometimes *anthelmintica*, etc.) with 4 per cent creosote, and the ethyl esters of the oil with 4 per cent creosote. (In some countries where good fresh oil is not available and ordinary ethyl esters tend to be irritant, iodization of esters by a special process is used.) The ethyl esters are more expensive but easier to inject, while the oil is cheaper but more difficult to inject because of its viscosity, which can, however, be reduced by warming the oil to body temperature. Supplies of oils and esters must be obtained from a reliable source.

Dosage.—For workers without great experience, the following dosage is recommended. Begin with 1 c.cm. and increase by $\frac{1}{2}$ c.cm. up to a dose of 5 or 6 c.cm. given once or twice a week. (Experienced workers may give larger doses in certain suitable cases and doses of 20 c.cm. a week or even more have been used.) If there is excessive local reaction or pain, the doses should be reduced or a different preparation tried. If reaction occurs, injections should be stopped completely until it has subsided, and then only small and very gradually increasing doses should be given.

Methods of injection.—The oil and ethyl esters are preferably given by a combination of intra-dermal and intra-muscular or subcutaneous injections.

Intra-muscular injections should be given deep into the upper part of the gluteus maximus muscle. Thorough massage of the part after injection assists rapid absorption. Subcutaneous injections are best given into the loose subcutaneous tissues of the fleshy parts of the limbs. By nearly withdrawing the needle and turning it in several different directions, up to 3 or 4 cubic centimetres can be given through one skin puncture.

Intra-dermal injections are given into the dermis of the lesions themselves. A special short intradermal needle is advisable. The needle is inserted at an acute angle, about two millimetres into the skin, and about 0.1 c.cm. is injected, raising a weal about one-third of an inch in diameter in the skin. Injections should be given into the corium and not just beneath the epidermis. Similar injections are given at about half-inch intervals over the whole lesion to be injected. The small swellings at the site of injection should subside in two or three days, and the lesion should not be injected a second time until a month has elapsed.

If all the lesions have recently been intra-dermally injected, the other two methods should be used. Usually not more than two or three cubic centimetres are given by intra-dermal injection at one time, the remainder (if any) of the dose ordered being given by other methods.

The intra-dermal method is suitable for injections into the macules of the neural type and into the lesions of the lepromatous type. Good results have also been reported with injections given near and around the affected nerve trunks and into the skin and subcutaneous tissue in their distribution.

Duration of treatment and assessing results.—The duration of treatment depends on the type and severity of the disease. In slight cases of the tuberculoid variety, signs of activity may disappear in a few weeks or months. In more marked neural cases, treatment may be prolonged and in the lepromatous cases treatment may need to be very prolonged. There are some patients in whom treatment appears to do little or nothing towards controlling the disease. Treatment should be continued until signs of activity have been absent for at least six months, preferably one or two years, and the patient is then kept under observation so that any tendency to relapse may at once be detected, and treatment resumed.

In assessing results of treatment, accurate records of clinical and bacteriological findings are needed. Care must be exercised to avoid attributing the subsidence of a reaction to treatment. In suitable cases, if treated properly, the progress of the disease is arrested and no new lesions appear; the lesions already present become less noticeable and may disappear; the anæsthesia may become less extensive; and the bacilli, if previously present in the skin, become less numerous and finally disappear. There are, however, often found permanent areas of anæsthesia and sometimes permanent deformities, although the disabilities caused may be minimized by treatment as described later.

Other forms of special treatment.—As already stated, hundreds of remedies have at one time or another been used and advocated in the treatment of leprosy and every year sees additions to this number. The common sequence of events is as follows. Some worker tries a new remedy and, to begin with, reports excellent results and advocates its wide adoption; later workers fail to confirm the value of the new treatment; and eventually the originator of the new treatment himself abandons it and finds that the good results originally obtained were largely psychological, or else obtained in cases in which clinical improvement is often seen even without treatment.

While it cannot be stated that no treatment other than hydnocarpus oil is of any value in leprosy, it can be stated that the value of other treatments has not been so marked as to justify their continued and widespread use. It is possible to mention here only a few of the treatments which have been used.

Numerous workers have used injections of preparations of heavy metals, particularly *gold*, and have reported some benefit in the disease in general and also in certain manifestations of the disease, such as eye affections, but other workers have failed to confirm this.

Potassium iodide administered by the mouth, with gradual increase from small to large doses, has been used by various workers during the last sixty years. Some workers have considered it of value in some cases; other workers have considered it of little or no value; but all workers are agreed that the administration of potassium iodide (which has often the specific effect of inducing a condition indistinguishable from lepra reaction) is a procedure which may in some cases produce harmful effects. The resolution of the International Conference of Leprosy, Cairo, 1938, on this matter reads as follows:—

‘With regard to treatment with potassium iodide, the use of this drug is frequently followed by disastrous results. It is therefore to be discouraged for the purposes of diagnosis, treatment, or as a test of recovery unless in very skilled and experienced hands’.

Various workers have used *vaccines* consisting of supposed cultures of *lepra bacilli*, or else sera produced by 'immunizing' animals with these vaccines, or with material obtained from leprosy patients. Examples of these preparations are Rost's 'leprolin' and Reinstein's serum. The results of such treatment are not striking.

Ever since their introduction, from time to time *aniline dyes* have been used in the treatment of leprosy. Certain dyes are definitely localized in the leprosy lesions after intravenous injections, and lesions may break down, ulcerate and then heal after large doses, but permanent improvement is usually not seen.

Various workers have reported beneficial results from the administration of preparations containing large amounts of one or more of the different *vitamins*. Reports of this form of treatment are very contradictory, and their value has not been proved.

One of the latest new treatments for leprosy has been the injection of *diphtheria-formol-toxoid*. The strikingly beneficial results originally reported have been confirmed by no one, and some workers find the treatment definitely harmful.

The induction of a high temperature either in the lesions themselves or in the patient's body as a whole has been used by various workers, and various methods of *heat therapy* have been employed, but the results are not striking or consistent.

Local treatment of lesions.—In addition to the local treatment discussed later under 'Management of complications', various forms of local treatment of the lesions themselves may be used.

All workers are agreed on the value of local irritation to lesions of all types, and some of the benefit produced by injection of *hydriocarpus* preparations may be caused by this local irritation. Various other forms of irritant have been used, such as carbon dioxide snow, but a very useful and more widely practicable measure is the application to the lesions of *trichloroacetic acid*. Solutions of the crystals in water of varying strengths from 1 in 1 to 1 in 4 (by weight) are used. The stronger solutions are used for touching nodules and other small but prominent lesions; the weaker solutions are used for application to larger areas of skin, infiltrations, patches, etc. The solution is applied with a small cotton-wool swab held in forceps, and the application should be followed by whitening of the skin and desquamation, but not by ulceration. A little experience is necessary in judging how much solution to apply and in what strength, and care is needed to avoid burning the skin, with the production of scars and sometimes keloids.

Another form of local treatment is the **surgical removal** of suitable lesions suitably situated. If the only lesion of leprosy is a single small patch, surgical excision may be practised, and is usually not followed by recurrence if the original lesion is of the tuberculoid sub-type. Sometimes more than one such patch may be excised.

In other cases, prominent disfiguring nodules and infiltrations in various parts of the body can be surgically removed for cosmetic reasons. Pedunculated or prominent nodules on exposed parts of the body may be excised, greatly enlarged, infiltrated and nodular ears may be trimmed down to normal size, etc., and in this way the patient's appearance may be considerably improved. In making these excisions, particularly of ear tissues, allowance must be made for contraction produced by fibrosis when the incision heals.

Another form of local treatment is the *local treatment of lesions of nasal mucous membrane* which are very common and may be troublesome in cases of the lepromatous type. The nasal passages should be washed out several

times a day with a bland fluid such as normal saline, or with mild antiseptics, and local applications of mild caustics or stronger antiseptics can then be made to the actual ulcers present in the nasal septum. In this way, such ulcers will frequently be made to heal, the discharge of the lepra bacilli from the nasal mucous membrane can be much diminished or prevented, and the patient thus rendered much less infectious.

MANAGEMENT OF COMPLICATIONS

Reaction.—In the milder forms of reaction, particularly the tuberculoid reaction seen in neural cases, hospitalization may not be needed, and the reaction will subside in time without any treatment beyond the cessation of the administration of hydnocarpus preparations or any other medicament which may have precipitated the reaction. Concomitant diseases present such as malaria should be treated.

In the more severe forms of reaction, particularly in lepromatous cases, hospitalization is necessary for proper treatment.

The patient should be kept in bed, properly nursed and given suitable general treatment, diet, aperients, etc. Various forms of medicinal treatment of reaction have been recommended such as the injection of small doses of antimony in the forms of potassium antimony tartrate given intravenously, or of fougadin given intramuscularly and the administration of large amounts of alkalis. Some patients appear to respond well to these forms of treatment, but others do not. Complications present, such as eye affections, severe neuritis, respiratory obstruction, etc., should be treated as described later.

In time, the fever and the other symptoms will subside, and hydnocarpus treatment, when resumed, must be undertaken with great caution as to dosage.

Trophic lesions.—By care it is frequently possible to minimize, if not prevent, the development of trophic lesions in cases of leprosy. The lesions are the result of the damage to nerves, chiefly those supplying the feet and hands. Careful examination of patients may reveal marked infiltration of the ulnar or median nerves, of the peroneal or tibial nerves, and suitable treatment for this neuritis (*vide infra*) may minimize the nerve damage and the resulting trophic changes. Together with this, electric treatment and massage of muscles slightly paralysed, or likely to become paralysed, may be of value. For example, massage of the small muscles of the hand, and repeated and forcible extension of the fingers likely to become contracted, may much minimize the deformity of the hand commonly produced by ulnar nerve affection. The wearing of a splint at night to maintain the extension of the fingers may also be of value.

If the nerves supplying the hands and feet are seriously affected, steps should be taken to prevent injury to the hands and feet from undue pressure, from heat, and from trauma. Patients with anæsthetic hands should not be allowed to cook or do manual work in which injury to the hands is likely. Similarly the feet should be protected by comfortable well-fitting shoes, specially made if necessary, or adapted, to prevent pressure on points where trophic ulcers are likely to develop, such as the head of the first metatarsal or the os calcis.

If trophic lesions have developed, they may be reduced by the measures mentioned above, massage, movement, splinting, etc. Good results have been reported from the injection of hydnocarpus preparations around the affected nerve and into the area of the trophic lesion in its distribution.

The trophic ulcer, nearly always found on the foot, is a troublesome condition which will, however, almost always yield to suitable treatment.

The trophic ulcers of the foot are of two types; firstly the simple trophic ulcer of the sole without necrosis of bone; secondly, the trophic ulcer with necrosis of the underlying bone. In practice it is found that most trophic ulcers are of the second type.

In the absence of necrosis of the bone, the ulcer will usually heal if the patient is kept off his feet and suitable local applications are used. It is most important to prevent pressure of injury to the feet, by keeping the patient in bed or allowing him to walk only with the use of crutches, until the ulcer has finally healed. The ulcer should be kept dry and clean, and all thickened dead skin around it should be kept pared off, and the ulcer encouraged to heal from the bottom. Many different local applications have been recommended, but none appears to be of outstanding value. Most of the common antiseptics such as eusol and other chlorine antiseptics, and lysol and other coal-tar preparations, may be used for cleaning septic ulcers, but prolonged soaking in antiseptics is to be avoided. Antiseptic or bacteriostatic powders such as sulphanilamide may be used, and the ulcer may be sealed with elastoplast or plaster of paris, and the dressing changed at long intervals.

If bone necrosis is present the ulcer may heal temporarily, but not permanently unless the bone is removed or else discharges itself through the ulcer. The bone necrosis can usually be detected by the use of a probe in the sinus at the base of the ulcer, and sometimes the presence of dead bone can be detected by eliciting crepitus on forcible movement of the neighbouring joint. If possible the extent of the necrosis should be studied by x-ray examination.

The dead bone should be removed by operation, which should be carefully performed to avoid all damage to surrounding healthy tissue. Local anæsthesia is induced by infiltrations round all the nerves at the ankle. Incisions should always be made on the side or dorsum of the foot and not on the sole. In order to minimize deformity, only dead tissue should be removed. Since some secondary infection is usually present, it is inadvisable to close the incision by sutures.

Secondary infection of trophic lesions, often of a virulent nature, is not uncommonly seen, and, in the absence of proper surgical treatment, is one of the commonest causes of death in cases of leprosy. It commonly leads to acute cellulitis, necrosis or gangrene of the affected part. The virulent secondary infection may arise through a perforating ulcer, but also without any breach of the surface, apparently as the result of blood-borne infection settling in the devitalized tissues.

In the past, early and radical surgical treatment of these acute septic conditions has been practised in the form of amputation of digits, hand, foot, or limb, and has given excellent results; without such operations patients frequently die. Although nothing has yet been published, it appears that the use of the sulphanilamide group of drugs has markedly influenced the treatment of these conditions, has reduced the necessity for surgical treatment, or made less radical surgical treatment possible.

Treatment of trophic lesions of the feet by such operations as sympathetic ganglionectomy has given very disappointing results.

Once trophic ulcers have been made to heal, the preventive measures already outlined should be adopted to prevent recurrence.

Leprous eye affections.—In the lepromatous type of leprosy, slight chronic eye affection is frequently present and may attract little attention and cause little trouble, except in cases of reaction. In some patients, however, particularly in certain countries, severe leprosy eye affections are very common, and frequently cause blindness. Chronic or sub-acute leprosy irido-cyclitis should be treated along ordinary lines. The patient should

be kept in a darkened room or wear an eye shade, the pupil should be kept constantly and fully dilated with atropine and hot boric fomentations should be applied several times a day.

Leprous infiltrations of the conjunctiva interfering with vision may be dissected off. In some cases of chronic eye affection with adherent and contracted iris, iridectomy may improve vision, but it should only be performed in the absence of all signs of inflammation.

In cases of the neural type also, leprosy eye affections may demand special treatment. The eye affections are caused by the involvement of the fifth and seventh nerves. The bad results of dryness of the surface of the eye caused by the inability to close the eye may be minimized by instillation of oily preparations. **Corneal ulcer** if present should be treated along the usual lines. The inability to close the eye properly may be partly remedied by the surgical operation of **lateral canthorrhaphy**. Great care is needed in these cases to prevent the injury to the surface of the eye by foreign bodies, etc.

Severe neuritis.—This may be seen either during a reaction or apart from it, and is most common in the ulnar nerve. Palliative treatment includes such procedures as the injection of cobra venom to relieve the pain, local application of heat, etc., in the form of hot compresses or of diathermy. Subsidence is frequently seen following the operation for *removal of the nerve sheath* around the affected part of the nerve, which is frequently a limited portion of the ulnar nerve above the elbow. Such operations may also minimize subsequent deformity.

Respiratory obstruction.—Obstruction of the larynx may be caused either by the presence of marked lepromatous lesions, especially during the phase of reaction, in which case it is acute or sub-acute, or by the fibrosis which follows the healing of such lesions, in which case it comes on very gradually. In either case, **tracheotomy** is sometimes needed for the relief of this condition which may otherwise cause death. When the reaction has subsided, it may be possible to remove the tracheotomy tube, but the advisability of removal is doubtful, for subsequent reactions may necessitate replacement. In cases caused by fibrosis the tube has to be kept in permanently.

THE CONTROL OF LEPROSY

The control of leprosy should be based on knowledge of the epidemiology of the disease which has already been outlined.

General principles.—With the exception of one or two countries such as Norway, definite plans of anti-leprosy work aiming at the control of leprosy have not been applied on a wide scale until the present century. During the last forty years, however, a considerable amount of valuable experience has been gained, and the matter has been discussed in various national and international conferences of leprosy workers. The recommendations made here regarding leprosy control are in general accordance with these recommendations.

Leprosy is a contagious disease, and the main principle of control of leprosy is, or should be, the same as that applied to the control of other contagious diseases, namely, the prevention of contact. The general opinion is that the methods of treatment at present available, even if widely and efficiently applied, cannot control leprosy in the community, although they may do much to facilitate other control measures, since without the organization of careful and thorough treatment of cases of leprosy, no control measures are likely to be effective, for the co-operation of those suffering from leprosy will not be secured, nor the sympathy and support of the public.

In various countries where leprosy is found, the following measures have been adopted : notification; segregation of all infective cases; periodical examination of non-infective cases and of contacts; segregation of indigent persons with leprosy; prevention of persons with leprosy following certain occupations, appearing in public places and travelling in public vehicles; the separation of children; and the control of immigration of patients suffering from leprosy. Legal provision for the application of such measures is usually made.

Where the number of persons with leprosy is not unduly great, and where reasonable financial resources are available, the control of leprosy is usually attempted on the above lines on a compulsory basis. The isolation of infectious cases is usually arranged in institutions, but in some countries in favourable circumstances, home isolation has been allowed.

In many countries where leprosy is common, however, the large number of cases, the lack of financial resources, the lack of trained workers and the lack of public opinion to make the measures effective, have rendered it difficult or impossible to institute such control measures against leprosy on a compulsory basis, and the work that is done is along similar lines but on a voluntary basis.

Modifications of the older type of isolation measure have rendered isolation more popular, and have done much to encourage patients to report voluntarily for isolation. The old idea of the isolation of all cases of leprosy has been abandoned, and usually only infectious cases are isolated. Of great importance is the establishment of efficient treatment in the isolation institutions, with the discharge of a considerable number of patients on becoming non-infectious. In a few centres, arrangements have been made for men and women with leprosy to marry and live in leprosy institutions, usually of the colony type, under proper safeguards to prevent the infection of children. This may be done in one of two ways; either children born may be separated as soon as possible after birth as in the Philippine Islands, or else marriage is only allowed after the male has been sterilized as in Japan, such couples, however, being allowed to adopt leprous children.

In some countries where leprosy is common, the giving of alms to leprous beggars is widely practised as a religious duty, and large numbers are thereby encouraged to gain a living by wandering around the country begging. A considerable number of these beggars are infectious cases, and, while it is true that their contact with the healthy population is limited, the menace to public health cannot be ignored. Special institutions or separate sections of leprosy institutions may be needed to deal with this problem, since the management of these persons demands measures differing from those framed for patients from the general population.

Practical application of these principles : Preliminary measures.—Before undertaking leprosy control measures in any area or country, the following preliminary steps should be taken :—

1. The appointment of a small group of suitable workers with the necessary knowledge and training in leprosy work to make a preliminary study of the problem. If trained workers are not available, suitable men are appointed and delegated for training at a suitable centre, and if necessary sent abroad for this purpose.

2. The carrying out by this trained staff of a general survey of the extent, the nature, and the severity of the leprosy problem in the area to be dealt with.

3. The framing of a leprosy control scheme to be based on the general lines outlined below, and the framing of suitable legislative support for the scheme.

Main lines of work.—These consist in leprosy surveys, diagnostic and treatment clinics, provision for isolation of infectious cases in institutions or in the patients' homes and villages, provision of social services for patients and dependants, the organization of propaganda work, and of thorough training for staff engaged in the work.

(a) **Leprosy surveys.**—In addition to the general preliminary survey of the problem, more intensive surveys are needed in the areas in which the work is undertaken. Methods of survey cannot be discussed here; they are described in the special report mentioned in the bibliography.

(b) **Diagnostic and treatment clinics.**—Such clinics may be established in suitable institutions or hospitals, but particularly in rural areas with few hospitals, they may need to be separate. The clinic should be properly staffed, and the work of the clinic should include the detection of all cases of leprosy in the area served by the clinic, if necessary by properly organized surveys; the treatment of cases of leprosy detected; the reporting to the authority concerned regarding infective cases detected; arranging for the isolation of such cases either at home or in institutions; periodical examination of infectious cases discharged from isolation; periodical examination of contacts of infectious cases; the organization of teaching for patients and contacts, and for the general public in the area served by the clinic.

(c) **The provision for isolation of infectious cases in institutions.**—Leprosy institutions may be of different kinds to meet different needs. In general, isolation should be provided at a central place, not remote from the areas from which the patients come. Colonies planned on the cottage principle are much to be preferred to the hospital type of institution, but in such institutions adequate facilities for all kinds of treatment and nursing should be available if needed. Institutions should preferably be in rural areas, well outside towns, and they should, if possible, be run to a considerable extent on the basis of partial self-government and partial self-support.

(d) **Provision for home isolation of infectious cases.**—The main point in home isolation is the prevention of contact between infectious cases and children and young people, and it is very doubtful whether home isolation should be allowed in houses where young people live and cannot be provided for elsewhere. Separate living and sleeping accommodation, eating, cooking utensils, etc., are needed, and are best provided in an annexe to the main dwelling and not in the main dwelling itself. The home isolated patient might in suitable circumstances undertake certain activities outside the home, agriculture, gardening, looking after cattle, etc., which do not involve contact with others. It is strongly recommended that home isolation if allowed should be supervised by regular inspection to see that the isolation is reasonably complete. In some circumstances, a small grant for maintenance of the home isolated patient may be needed, but should of course be contingent on the isolation being properly maintained. In some countries, group isolation of infectious cases in villages or small towns is preferable to individual isolation in homes. A plot of land on the outskirts of a village, suitable buildings, and arrangements for feeding and maintenance are required.

(e) **Provision of social services.**—These services are needed to aid patients themselves and the dependants of patients, particularly of isolated patients, who may be left unprovided for. Small grants for the maintenance of patients or their dependants may be needed, and special arrangements for the supervision, care and education for children of patients. Another activity of such services is the training of non-infectious patients, or of healthy children of leprous parents, for suitable occupations, and the securing of employment for such persons.

(f) **Provision of institutional accommodation for disabled non-infectious cases.**—A considerable number of persons of this type are usually found. They are non-infectious, but because of the presence of deformities of hands and feet, trophic ulcers, etc., they are permanently disabled. Compulsory isolation of these persons is not necessary, but some provision is needed for those unable to maintain themselves, and the condition of such patients frequently demands treatment, medical or surgical, and such facilities should be provided.

(g) **The organization of suitable propaganda to create the public opinion necessary for the success of the measures.**—This matter is of vital importance but cannot be discussed here.

(h) **The organization of facilities for thorough training of the medical staff engaged in the work.**—Theoretical and practical instruction should be included in the ordinary pre-graduate medical curriculum, but centres of thorough post-graduate training are also needed.

Organization.—The details of how such measures can be put into force and made effective, whether such work should be staffed by ordinary state medical or public health officers, or whether a special branch of such services should be formed to undertake the work, and what part voluntary agencies can play in such work, etc., cannot be discussed here, since conditions in different countries vary so widely. In most countries it has been found that the special nature of leprosy work demands the services of men of the right type specially selected and trained, but it is certainly advisable that the anti-leprosy service shall be a branch of the public health service. It is also found that voluntary organizations can do much to aid anti-leprosy work, particularly by undertaking activities of the nature of social aid to patients and their dependants.

In many countries where leprosy is common, the inauguration of a complete scheme of leprosy control along the above lines is impracticable, and in such circumstances an attempt should be made to concentrate on certain parts of the work which are of the greatest importance. It may for example be impossible to isolate all the infectious cases, and in such circumstances it is best to concentrate on preventing contact between infectious cases and children and young people. Infectious persons living in homes containing no young people may be left there, but from homes with infectious cases and young people, either the cases should be removed to an isolation centre, or else the children may be removed. Such children may be adopted by healthy relatives or others, or else admitted to special homes.

In some countries it will be found that leprosy is a really serious problem in only limited areas, and it may be advisable or necessary to confine work in these areas rather than to attempt to cover the whole country. In any case, anti-leprosy measures should be inaugurated to begin with in limited areas, and only when their practicability has been demonstrated should they be extended widely.

The results of anti-leprosy work.—The demonstration of the effectiveness of anti-leprosy measures is likely to take a long time. The long latent period of leprosy means that new cases will be found long after all infectious cases have been isolated. The effectiveness of anti-leprosy measures can best be demonstrated by a fall in incidence found in repeated thorough surveys, which may however not often be practicable. A very valuable indication of the effectiveness or otherwise of measures adopted may be obtained by a demonstration of the presence or absence of a fall in the incidence of leprosy in children on periodical examination of all school children in the areas. In some countries, the reduction in the incidence of leprosy has been demonstrated by the fall in the incidence in young men reporting for compulsory military service.

The results of compulsory isolation measures have varied markedly. In some countries, for example, Norway, where the serious leprosy problem of sixty years ago has almost entirely disappeared, and where public opinion gave strong support to the measures, the results appear to have been excellent. In some other countries, particularly where public opinion has not given the necessary support, the laws have been evaded and the measures have met with little success. In some countries, Japan and the Philippine Islands for example, a moderate degree of success appears to have been attained, but the work has not yet continued for sufficiently long to make possible a final judgment of its effectiveness. In Brazil a comprehensive scheme of leprosy control has recently been inaugurated, but it is too early to judge its results.

SELECT BIBLIOGRAPHY

Below is given a list of the main publications on leprosy, with a few notes on their nature, and also of the important references to the subjects named. To some subjects, however, the references are so numerous and scattered that it is impossible to detail them.

Textbooks.—The following books give a general account of leprosy. The first two are mainly of historical interest :—

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| Danielssen, D. C., and Boeck, W. | Traité de la Spedalskhed, Paris, 1848. |
| Hansen, G. A., and Looft, C. | Leprosy in its Clinical and Pathological (translated by Norman Walker). Aspects. John Wright, Bristol, 1895. |
| Jadassohn, J. | Lepra, Fischer, Jena, 1928. |
| Jeanselme, Ed. | La Lepre, Doin, Paris, 1934. |
| Muir, E. | Leprosy, Diagnosis, Treatment and Prevention (Sixth Edition), Indian Council, British Empire Leprosy Relief Association, Delhi, India, 1938. |
| Rogers, L., and Muir, E. | Leprosy (Second Edition). John Wright, Bristol, 1940. |

The last book named is the most comprehensive.

Reference book :

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| Klingmuller, V. | Die Lepra, Julius Springer, Berlin, 1930. |
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This book abstracts practically all publications on leprosy up to that date. A later volume covers more recent years.

Periodicals :

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| Lepra Bibliotheca Internationalis (Leipzig), 1900-1914—Quarterly. |
| International Journal of Leprosy (Manila, Philippine Islands), 1932—Quarterly. |
| Leprosy Review (London), 1930—Quarterly. |
| Leprosy in India (Calcutta), 1929—Quarterly. |
| La Lepre (Japan), 1930—Quarterly. |
| Revista Colombiana de Leprologia (Colombia), 1939—Quarterly. |
| Revista Brasileira de Leprologia (Brazil), 1933—Quarterly. |
| Leprosy, Summary of recent work (From Tropical Diseases' Bulletin), British Empire Leprosy Relief Association, London—Periodically. |

The above-mentioned books contain numerous references to subjects mentioned below, but in addition the following references should be mentioned, and there are many others scattered throughout the literature.

History of leprosy :

- | | |
|----------------|---|
| Hensler, P. G. | Vom abendlandischen Aussatze in Mittelalter Hamburg, 1790. |
| Kaposi | Leprosy in 'Hebra on skin diseases', New Sydenham Society, London, 1874. |
| Simpson, J. Y. | Antiquarian notices of leprosy and leper hospitals in Scotland and England, Edinburgh Med. and Surgical Jour., 1841-42. |
| Virchow, R. | Archiv, XVIII 1860, XX 1861. |

- Newman, G., and others .. Prize essays on leprosy, two volumes, New Sydenham Society, London, 1895.
 Lowe, J. Comments on the history of leprosy, Indian Med. Gaz., 77, p. 680, 1942.

Distribution.—Numerous references in textbooks and leprosy literature and

- de Souza-Araujo, H. C. .. Leprosy survey made in forty countries (1924-1927), Rio de Janeiro, 1929.

Bacteriology :

- McKinley, E. B. Medicine, 13, p. 377, 1934.

This is the best single review of the subject.

Susceptibility and immunity and the Mitsuda test :

- Mitsuda Jap. Jour. of Urol. and Derm., 1916.
 Hayashi, F. Internat. Jour. Leprosy, p. 31, 1933.
 Dharmendra, Lowe, J., and others Studies of the lepromin test. Leprosy in India, 1940, p. 121; 1941, pp. 40, 77, 81, 89; 1942, pp. 4, 86, 93, 122.
 Rotberg, A. Rev. Bras. Leprol., 5, p. 45, 1937.

Symptomatology and classification :

Good accounts are given by Rogers and Muir, and by Muir. In addition the following two reports should be consulted: Report of the Leonard Wood Memorial Conference on Leprosy, Manila, Philippine Islands, 1931, and Report of the International Leprosy Congress, Cairo, 1938.

Pathology.—Numerous references scattered throughout the literature. For tuberculoid changes see numerous articles by Wade in the International Journal of Leprosy.

Treatment :

- Muir, E. Internat. Jour. Leprosy, 1, p. 407, 1933.

A good review of the subject.

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